Quadruple primary neoplasms in a 27-year-old woman

HPS Wai, TK Yau, WM Sze, MW Yeung, AWM Lee

CASE REPORT

A 27-year-old woman was referred to our department on 3 February 1998 with a diagnosis of malignant melanoma associated with cystic teratoma of ovary. She had had a laparotomy and bilateral salphingo-oophorectomy on 5 January 1998. Pathology revealed tumour involvement of left ovary, left parametrium and malignant ascites, the right ovary showed polycystic disease, the uterus showed simple hyperplasia of endothelium, the omentum had no tumour and subdiaphragmatic scrapping was negative. On histological examination of the tumour, the cystic portion was basically a cystic teratoma with presence of skin, glial and bony tissue, the solid portion consisted of sheets of undifferentiated tumour cells, which on immunohistochemical staining shown strong positivity to HMB 45 and S-100. Ultrastructual examination confirmed melanocytic differentiation.

Her chest X-ray was clear. Computed tomography of abdomen and pelvis suggested bilobar liver metastasis and significant para-aortic lymphadenopathy. The alpha-fetoprotein (αFP) and beta-human chorionic gonadotrophin (β-hCG) were within normal limits. The diagnosis was a malignant melanoma arising in cystic teratoma of ovary, stage IV disease.

Her past medical history included multiple primary neoplasms. She had right thigh cutaneous histiocytoma at the age of 20 years, with complete excision performed. She developed poorly differentiated invasive ductal carcinoma of left breast (stage pT2N0M0) at the age of 21 years and had a left mastectomy and left axillary clearance; no postoperative adjuvant treatment was given. She also recently had multiple thyroid nodules which shown atypical cells, suggestive of a follicular neoplasm, and total thyroidectomy was contemplated.

Evaluation of her family revealed a strong family history of malignancy. Her twin sister died of a primary brain tumour at the age of 8 years. Her father died of lung cancer at the age of 45 years. Her paternal grandfather died of lung cancer in his 60s. Her paternal grandmother died of primary liver cancer in her 60s. One of her paternal half-uncles (mutual grandfather, different grandmothers) died of a primary brain tumour in his 50s while another died of lung cancer in his 70s. There was no positive family history of malignancy on her maternal side (*Figure 1*).

She was treated with combination chemotherapy using cisplatin (75 mg/m^2) and cyclophosphamide (750 mg/m^2). However, she deteriorated rapidly after the first cycle of chemotherapy and died on 16 March 1998.

INTRODUCTION

The familial effects of cancer are consistent with the idea that individuals may possess a genetic susceptibility to cancer in general (Ahlbom et al, 1997). It has been suggested that inherited genetic background might play an important role in the tumorigenesis of primary malignant neoplasm in younger patients whereas epigenetic factors would be more important in older patients.

This report details a young patient who developed four primary neoplasms with association of a strong family history of malignancy. This clinical feature is compatible with a familial cancer syndrome.

DISCUSSION

Malignant melanoma arising within cystic teratoma of ovary is exceedingly rare. Up to 1995, only eight cases have been reported in the literature. Previous cases generally occurred in older individuals, usually with a poor outcome. Following aggressive surgical resection, platinum-based chemotherapy is usually given.

Overall, 50% of patients with stage I dermoid-associated melanoma were alive at 2 years, compared with 89% of patients with stage I dermoid-associated squamous cell carcinoma at 5 years. In the last 10 years, however, with the application of aggressive chemotherapy, survival has improved (Davis, 1996). There was also one report of primary malignant melanoma arising in a cystic teratoma of the ovary which recurred 4 months after surgery responded completely to immunotherapy using intramuscular injection of OK-432 (Tsukamoto et al, 1986).

The patient reported here developed four independent benign and malignant tumours within an interval of 7 years (from the age of 20–27 years). Association with an underlying familial cancer syndrome is a possibility. In fact, these clinical features highly resemble those of Li–Fraumeni syndrome, a familial cancer syndrome in which affected relatives develop a diverse set of early-onset malignancies including breast carcinoma, sarcomas and brain tumours (Frebourg et al, 1995).

The Li–Fraumeni syndrome was initially described in 1969 in a retrospective epidemiological review of more than 600 paediatric sarcoma patients (Malkin, 1993). The clinical definition of the syndrome has been refined in the last two decades by prospective analysis of several families. Despite these exhaustive studies, the gene or genes responsible for the usual constellation of tumours in these families remain elusive until 1990, when it was demonstrated that germ-line abnormalities of the p53 tumour suppressor gene could account for the occurrence of cancer in many classic Li–Fraumeni families (Malkin, 1993).

Dr HPS Wai is Medical Officer, **Dr TK Yau** is Consultant, **Dr WM Sze** is Senior Medical Officer, **Dr MW Yeung** is Senior Medical Officer and **Dr AWM Lee** is Consultant in the Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong

Correspondence to: Dr HPS Wai

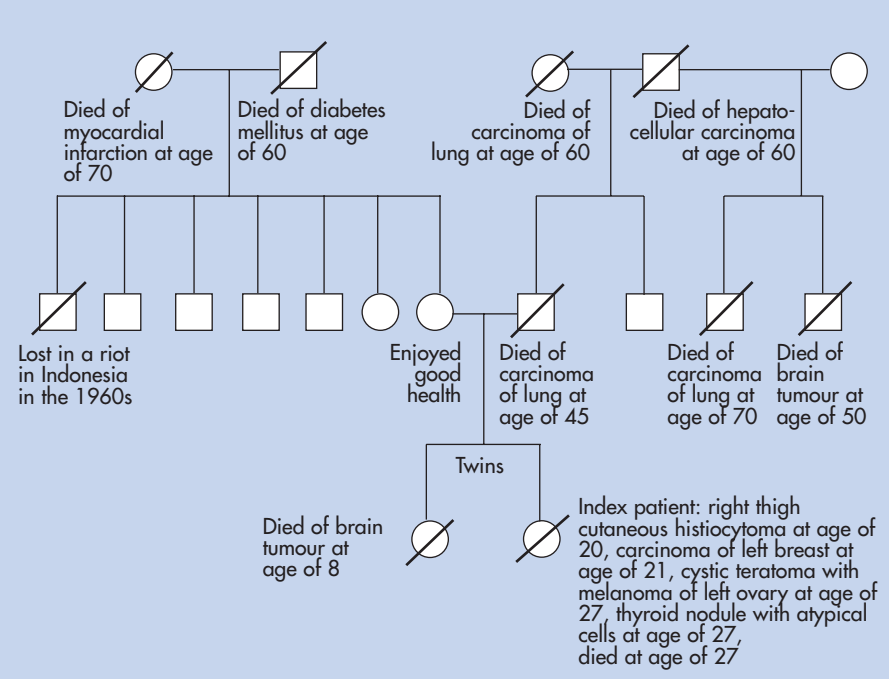

Figure 1. Family tree of the patient.

p53 is the most frequently mutated gene in human cancer cells. Its wild type codes for a protein with pivotal functions, namely interaction with key components of the cell cycle leading to cell cycle arrest and induction of programmed cell death, or apoptosis (Neubauer et al, 1996). The mutation of an allele on the p53 gene with loss of the healthy allele is associated with the occurrence of cancer. Indeed, the mutated p53 protein loses its antiproliferative properties, favouring a deregulation of cellular multiplication with the accumulation of genetic aberrations.

The homozygous deletion of the p53 gene in germ cells in members of certain family cancers (Li–Fraumeni syndrome) leads to an increased incidence of cancers in the child or young adult (Zalcman et al, 1994). The gene has been found to be associated with breast cancer, soft tissue sarcoma and less commonly benign soft tissue tumours, brain tumours, melanoma, ovarian cancer, leukaemia, osteosarcoma and adrenal cortical cancer.

Cancer is considered to be a multifactorial disease in which a host cell is transformed from normal to malignant as a result of complex interactions of external (environmental) stimuli and cancer-predisposing or cancer-suppressor genes. Mutations in the tumour suppressor gene occur in >50% of human malignancies (Boman et al, 1993). Not infrequently, cancer is found to aggregate in families in an apparently non-random fashion. Both common and rare tumours may occur together in familial cancer families. Frequently, tumours occur at an earlier age than one would expect in the general population; often, multiple tumours of different organs develop in a particular affected family member (Malkin, 1995). In familial cancer a germ-line mutation is passed on in an autosomal dominant pattern, but cancer will develop in people who inherited the defect only if other mutations also occur in susceptible somatic cells.

Studies have shown that individuals may possess a genetic susceptibility to cancer in general (Ahlbom et al, 1997). In a population-based study in Sweden, cancer risk in the offspring was increased by about 1.1 times when the father had cancer, whereas no increase was noted when the mother had cancer. If both parents had cancer, the risk for sons was 1.39 and for daughter 1.34. Cancer in both parents increases cancer risk in the offspring at many sites. Chance and environmental effects may explain some of the results, but true genetic factors probably contribute to the majority of the increased incidence (Hemminki and Vaittinen, 1997).

The prognostic implication of familial cancers still remains unclear. Recent advances in identification of genetic abnormalities associated with certain types of cancer have stimulated the development of screening and counselling programmes for hereditary and familial forms of cancer (Bleiker et al, 1997). In USA and Europe, familial cancer clinics are being established. However, genetic screening also leads to complex ethical, social and legal implications. Because there are no outcome data on which to base practical guidelines for genetic screening or management of asymptomatic carriers in families at risk, testing should be restricted to research settings (Cole et al, 1996). **HM**

Ahlbom A, Lichtenstein P, Malmstrom H, Feychting M, Hemminke K, Pedersen NL (1997) Cancer in twins: genetic and non-genetic familial risk factors. *J Natl Cancer Inst* **89:** 287–93

Bleiker EM, Aaronson NK, Menko FH et al (1997) Genetic counseling for hereditary cancer: a pilot study on experiences of patients and family members. *Patient Educ Couns* **32:** 107–16

Boman F, Peters J, Ragge N, Triche T (1993) Infrequent mutation of the p53 gene in fibrous tumors of infancy and childhood. *Diagn Mol Pathol* **2:** 14–22

Cole DE, Gallinger S, McCready DR, Rosen B, Engel J, Malkin D (1996) Genetic counseling and testing for susceptibility to breast, ovarian and colon cancer: where are we today? *CMAJ* **154:** 149–55

Davis GL (1996) Malignant melanoma arising in mature ovarian cystic teratoma (dermoid cyst). Report of two cases and literature analysis. *Int J Gynecol Pathol* **15:** 356–62

Hemminki K, Vaittinen P (1997) Effect of paternal and maternal cancer on cancer in the offspring: a population-based study. *Cancer Epidemiol Biomarkers Prev* **6:** 993–7

Frebourg T, Barbier N, Yan YX et al (1995) Germ-line p53 mutations in 15 families with Li–Fraumeni syndrome. *Am J Hum Genet* **56:** 608–15

Malkin D (1993) p53 and the Li–Fraumeni syndrome. *Cancer Genet Cytogenet* **66:** 83–92

Malkin D (1995) Age-specific oncogenesis: the genetics of cancer susceptibility. *Environ Health Perspect* **6:** 37–9

Neubauer A, Thiede C, Huhn D, Wittig B (1996) p53 and induction of apoptosis as a target for anticancer therapy. *Leukemia* **10** (suppl 3): S2–S4

Tsukamoto N, Matsukuma K, Matsumura M, Kamura T, Matsuyama T, Kinjo M (1986) Primary malignant melanoma arising in a cystic teratoma of the ovary. *Gynecol Oncol* **23:** 395–400

Zalcman G, Tredaniel J, Lechapt E, Lubin R, Soussi T, Hirsch A (1994) The p53 gene and protein in bronchial carcinogenesis: from biological to clinical aspects. *Rev Mal Respir* **11:** 455–72