

with assisted ventilation. There are a number of other cases, along with our patient, that seemed to have recovered from severe tetrodotoxin poisoning with no permanent sequelae despite the apparent features suggesting hypoxic brain damage.

This case serves as a reminder to us that puffer fish poisoning is not entirely unknown in Malaysia, although the most recently reported cases have come from East Malaysia rather than Peninsular Malaysia<sup>2,3</sup>. Our case was initially complicated by the lack of detailed history concerning exactly what she had eaten and this nearly led to us abandoning supportive therapy at an early stage. The lesson we must learn

from here is that supportive care should be maintained while strenuous efforts are being made to establish any potentially reversible causes, especially in a case where the aetiology of the cerebral insult is not well defined. Furthermore, in patients with suspected tetrodotoxin poisoning, we strongly recommend that resuscitative treatment be continued even in the presence of signs suggestive of brain death.

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## Second Malignant Neoplasms: An Increasingly Recognized Complication of Childhood Cancer

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### Summary

Second malignant neoplasms (SMN) are an increasingly recognized late complication seen in childhood cancer survivors. A total of 3 cases of SMN have been found in the Department of Paediatrics, University Hospital Kuala Lumpur after a 15-year experience of treating childhood malignancies. Two cases are described here. The first developed abdominal non-Hodgkin's lymphoma 3 years after undergoing an allogeneic bone marrow transplant for second relapse of acute lymphoblastic leukaemia, while the second child developed myeloid leukaemia two years after completing treatment for acute lymphoblastic leukaemia. Progress in the management of childhood cancer in Malaysia and the availability of bone marrow transplantation facilities have increased the number of childhood cancer survivors; leading to increased incidence of SMN.

*Key Words:* Second malignancy, Late complications of childhood cancer, Cancer

## Introduction

The management of childhood cancer in Malaysia has markedly progressed with advances in facilities for diagnosis and the availability of multiagent therapy for treatment. Two centres are available locally for paediatric bone marrow transplantation and this further increases the number of children surviving from cancer.

With longer follow-up, a few children have been found to have developed second malignant neoplasms (SMN). Although only a small number of cases have been identified, this represents an emerging problem which will affect the child, his family and the physicians managing him.

We highlight here two cases of second cancers which developed between 2 and 7 years after the patients achieved remission from their primary malignancies.

## Case Reports

### Case 1

THY first presented in 1988 at the age of 7 years with a 4-week history of fever, progressive pallor and spontaneous bruising. She had hepatosplenomegaly and generalized lymphadenopathy on examination. FBC at diagnosis was Hb 50g/L, platelet  $28 \times 10^9/L$  and TWBC  $67 \times 10^9/L$ , with 94 % blasts in the peripheral film. Bone marrow examination confirmed the diagnosis of acute lymphoblastic leukaemia, FAB - L1. No immunophenotyping facilities were available at that time. There was no family history of cancer. She received chemotherapy using the Berlin-Frankfurt-Munster (BFM) protocol which consisted of vincristine, daunorubicin, prednisolone, asparaginase, cyclophosphamide and cytosine arabinoside for induction. She also received intra-thecal methotrexate and cranial irradiation of 1800 Gy. She attained remission and completed the 2-year chemotherapy course in 1990.

She remained well till 1992, when she developed a 2-week history of fever and petechiae. Bone marrow examination confirmed relapse and she achieved a second remission following a further 2 years of chemotherapy following the BFM relapse protocol.

However, 9 months after stopping chemotherapy, she presented with a short history of vomiting and persistent headache. Lumbar puncture revealed blasts in the CSF. The bone marrow was not affected. The isolated CNS relapse was treated using the modified Boston protocol which consisted of prednisolone, vincristine, asparaginase and high-dose methotrexate. She also received craniospinal irradiation. Following remission, she successfully underwent an allogeneic bone marrow transplantation with busulphan, melphalan and cyclophosphamide conditioning and remained in continuous complete remission thereafter.

However in 1995, at the age of 14 years, she presented to the gynaecological outpatients' clinic with a 4-week history of abdominal pain. A hard suprapubic mass was palpable which was fixed to the anterior rectal wall. At laparotomy, a large inoperable pelvic tumour was found. Histopathological examination of the biopsied tissue showed loss of nodal architecture with infiltration by malignant lymphoid cells. Immunostaining showed that these neoplastic cells were of B phenotype. Examination of the bone marrow and CSF showed no abnormality. She was then given the first course of chemotherapy for Stage III B-NHL which consisted of vincristine, ifosfamide and high-dose methotrexate.

However, she developed severe neutropenia and expired shortly of septicæmic shock.

### Case 2

NS, was first seen in 1992 at the age of two years with the complaint of persistent fever and progressive pallor for 2 weeks. Clinically, she was markedly pale with generalised lymphadenopathy and the liver was 2 cm palpable. Full blood count at presentation was Hb 32g/L, platelets  $40 \times 10^9/L$  and TWBC  $15.7 \times 10^9/L$ . Bone marrow examination revealed 90% lymphoid blasts of FAB L1 morphology. Peroxidase staining was negative. Immunophenotyping facilities were not available then. There was no mediastinal mass on chest radiography and lumbar puncture confirmed no CNS infiltration. She was treated using the BFM - ALL protocol. Remission was successfully induced and she remained well, completing her maintenance chemotherapy two years after starting treatment.

In 1996, at the age of 6 years, she developed fever and

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bruises over a 2-week period. On examination there was pallor and hepatosplenomegaly. FBC showed Hb 64g/L, platelets  $32 \times 10^9/L$  and TWBC  $72 \times 10^9/L$  with 11% blasts and 10 % eosinophils in the peripheral blood film. Bone marrow examination revealed 90% myeloblasts of FAB M4 morphology with an excess of eosinophils. Peroxidase staining was positive. These blasts expressed CD 13 (74%) and CD 33 (73 %) while B and T cell markers were negative. She commenced chemotherapy following the BFM - AML protocol, which consisted of cytosine arabinoside, daunorubicin and etoposide in the induction phase. However, she did not achieve remission. Bone marrow examination after consolidation phase of chemotherapy revealed 30 % blasts. The parents then refused further chemotherapy in view of the poor overall prognosis, and opted for palliative treatment.

### Discussion

Second malignant neoplasms (SMN) are an increasingly-recognised late complication of childhood cancer. The advances in diagnosis, staging, treatment plus the use of multimodal and intensive multiagent therapy have increased the number of survivors of childhood malignancies. However, this is associated with an increase in the incidence of SMN.

The predicted incidence of developing SMN ranges from 3.3 % to 35 %<sup>1</sup>; the wide variance is explained by the long follow-up time required to determine the incidence of second malignancies. Patients with acute lymphoblastic leukaemia, the commonest childhood cancer, have an actuarial risk of 2.5 % of developing a second malignancy. The cases reported here are 2 out of 3 cases of SMN seen in the paediatric department of UHKL after a 15-year experience of treating childhood malignancies.

A wide variety of SMN have been reported including rare tumours eg melanomas thyroid tumours and squamous cell carcinoma. In a 40-year review by Smith *et al*, the most common primary malignancies were lymphomas followed by soft-tissue sarcomas and retinoblastoma. The commonest second malignancies were osteosarcoma, soft-tissue sarcomas and leukaemia<sup>2</sup>.

Many risk factors have been identified in the aetiology of SMN. Treatment - related factors include alkylating

drugs, anthracyclines and irradiation; agents that both our patients were exposed to in the course of their treatment. Cyclophosphamide is an established carcinogen especially to the bladder. A 4.5 - fold risk of developing bladder cancer following treatment of non-Hodgkin's lymphoma with cyclophosphamide was reported by Travis *et al*<sup>3</sup> and recommended that the use of this carcinogenic agent for non-neoplastic diseases may need reevaluation. Alkylating agents have also been implicated in the development of haematological malignancies in patients cured of Hodgkin's disease. Seventeen of 19 patients reviewed by Smith who developed leukaemia (especially erythroleukaemia, FAB M6 lineage) received an alkylating agent when treated for their primary cancer<sup>2</sup>.

Recently, doxorubicin has been identified as a possible risk factor in the development of secondary acute myeloid leukaemia. It has also been suggested that the leukemogenic potential of anthracyclines may be synergistic with that of alkylating agents. Other chemotherapeutic agents that have been identified to carry risk of SMN include epipodophyllotoxin and cisplatinum.

Radiotherapy, while significantly improving long-term survival in some childhood cancer patients, has resulted in an increasing incidence of SMN. Both high and low-dosage radiation therapy have been implicated as carcinogens with a 5 to 10-fold increase in the number of SMN seen. Many radiation-induced malignancies usually appear after ten years and occur within or near the irradiated field. Osteosarcoma, thyroid cancer and soft tissue sarcomas are the commonest second malignancies to occur in previously irradiated tissue.

Hepatocellular carcinoma and soft tissue sarcomas developing in irradiated post-nephrectomy renal beds of children cured of Wilms' tumour have also been reported.

Genetic predisposition to malignancy has also been implicated as a risk factor for the development of SMN. Studies of these affected patients have helped identify genetic abnormalities such as mutations of the tumour suppressor gene p53 which predispose patients and their families to multiple cancers especially osteosarcoma and breast cancer. Patients with retinoblastoma have a 500-fold higher risk of developing soft-tissue or bone

sarcoma compared to the general population. Ninety percent of patients with retinoblastoma who develop a second cancer have chromosome 13 q 14 deletions. The RB gene for retinoblastoma is associated with a 35 % incidence of developing a second cancer during the lifetime of the survivor.

We feel the SMN in Case 2 may have been due to exposure to cyclophosphamide and doxorubicin. While in Case 1 apart from the above factors, the patient also underwent spinal irradiation and a prolonged period of immuno - suppression with bone marrow transplantation ; failure of immunosurveillance is a known predisposition to cancer.

The prognosis of patients developing a second malignancy is poor. In the review by Smith<sup>2</sup>, only a third of the 162 patients who had SMN were cured. While in our experience , both our patients died

without achieving remission from SMN. The poor outcome is postulated to be due to the more aggressive biology of these tumours plus the sites of occurrence that prohibit local resection. The more aggressive nature of these neoplasms have been attributed to DNA damage resulting from irradiation or use of alkylating drugs.

The development of a second malignancy is a serious complication of childhood cancer and can be devastating to both the child and his family . It is imperative that survivors of childhood malignancies be followed-up for many years. Modifications of treatment protocols should be made to minimise the carcinogenicity of therapy while preserving efficacy. With the improvement in treatment for paediatric cancer patients in Malaysia, we should be alert to anticipate increasing incidence of SMN.

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