CASE REPORT

A Rare Case of Li Fraumeni Syndrome Cancer Family Syndrome

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Summary
A 26-year-old female presented with osteosarcoma of the rib. Three years later, her 16-year-old brother developed osteosarcoma of the right tibia.

They belong to a family with a strong history of various types of cancers. The disease pattern is similar to a rare familial cancer disorder known as Li Fraumeni Syndrome. To the best of our knowledge this is the first reported family with Li Fraumeni Syndrome in Malaysia.

Key Words: Li Fraumeni syndrome, Osteosarcoma

Introduction
There is much interest in the study of genetic susceptibility to cancer. Historically there are several clearly defined cancer family syndromes, including Puertz Juerger Syndrome, Neurofibromatosis and Polyposis Coli. Li-Fraumeni Syndrome (LFS) was first described by Li FP and Fraumeni JF in 1969. It is an inherited form of cancer, affecting children and young adults, and characterized by a wide spectrum of tumours, including soft tissue and bone sarcomas, brain tumours, adrenocortical tumours and premenopausal breast cancers. This syndrome is rare compared to the other types of cancer family syndromes. We report two siblings who presented with osteosarcoma from a family with a strong history of various malignancies.

Figure 1: Osteosarcoma of the rib
Case 1

A 26-year-old Chinese girl developed swelling of her right lateral chest wall for 2 months. This was associated with pain and weight loss. There was no history of cough or haemoptysis. Radiographs showed an osteoblastic lesion of the right 7th rib (Figure 1). An open biopsy confirmed the diagnosis of osteosarcoma. There was no evidence of metastasis on the CT scan of the chest. She was given neoadjuvant chemotherapy followed by wide resection of a segment of the 7th rib. Postoperatively another 3 courses of chemotherapy were delivered. She is disease free on last review three years after surgery.

![Figure 2a: Periosteal osteosarcoma of the tibia](image)

X-ray of the affected tibia showed an osteoblastic lesion of the diaphyseal region (Figure 2a). Presence of Codman's triangle and sunburst appearance of the lesion suggested osteosarcoma and it was confirmed by a needle biopsy. CT scan of the chest showed no pulmonary metastasis.

![Figure 2b: Post-operative xray with allograft and nailing](image)

Case 2

A 16-year-old Chinese boy who is the younger sibling of the Case 1 presented with a progressively enlarging swelling of the upper right tibia for 4 months duration. This was associated with moderate pain with no fever, weight loss or loss of appetite.

Wide excision of the tumour was performed after 3 courses of neoadjuvant chemotherapy. The bone deficit was reconstructed with an intercalary allograft stabilised by interlocking nail fixation (Figure 2b).

Post-operative period was uneventful and he completed the chemotherapy regime. The boy returned to the institution about 6 months after surgery for sudden onset of left-sided weakness. MRI revealed a large brain tumour which is likely to be of primary origin. The family refused further intervention and decided to seek traditional treatment.
Discussion

In 1969 Li and Fraumeni described 5 families among a group of 648 children with rhabdomyosarcoma. They noted that within these families there was a high risk of premenopausal breast cancer and second malignancy. The pattern of inheritance was most likely to be autosomal dominant. The diagnostic criteria for this syndrome includes:

1. A proband aged under 45 years with a sarcoma, with a;
2. First degree relative aged under 45 years with any cancer and additional;
3. First or second-degree relative under 45 years with any cancer or sarcoma at any age.

Types of tumour in LFS spectrum include acute leukaemia, premenopausal breast cancer, brain and adenocortical tumours as well as bone and soft tissue sarcomas. Other studies have indicated that a number of other cancers may occur at an increased frequency in these families, notably melanoma, germ cell tumours, Wilms' tumours, gastric and pancreatic carcinomas and lung cancer.

Although the diagnostic criteria of this syndrome are well accepted, other researchers feel that it is too stringent. They suggest a more relaxed diagnostic criterion and coined the term Li-Fraumeni Like Syndrome (LFL). The diagnostic criteria includes:

1. Proband with any childhood tumour or sarcoma, brain tumour or adenocortical tumour under 45 years, plus
2. First or second degree relative with a typical LFS tumour at any age and another first or second degree relative with any cancer under the age of 60.

Germline mutations of tumour suppressor TP53 gene were thought to be the main underlying factor to develop LFS. Porter et al. reported on 17 patients with osteosarcoma and found two families, which fulfilled the diagnostic criteria for LFS. Both these families were shown to have the genetic alteration in the TP53 gene. Li et al. reported that 71% of patients with LFS had TP53 mutations. The TP53 encodes a transcriptional factor able to regulate cell cycle and apoptosis when DNA damage occurs. TP53 gene will halt the cell cycle in the G1-synthesis interface and
allow the DNA repair to take place. If the damage is irreparable TF53 will then initiate apoptosis.

The two siblings described in this report fulfilled the criteria needed for the diagnosis of LFS. There is a first degree relative under the age of 45 with a sarcoma and multiple second-degree relatives with various types of carcinomas and sarcomas (Figure 3).

Four out of 15 siblings of the patient's father had died below 45 years of age. Three others including father of the proband developed cancers in their fifties. It is interesting to note that those who developed cancers after the age of 50 years were all male while those with cancers below the age of 45 years were female with the exception of the proband. The pattern of transmission suggests an autosomal dominant inheritance as suggested in the literature. There seems to be a later clinical manifestation of cancer in males as compared to females. Although it is difficult to exclude incidental cancer in older members of the family, it is obvious that the father of the proband did transmit the condition to his offspring although his manifestation of cancer was at 52 years of age. Unfortunately we do not have any facilities to analyse the genetic components at this stage.

References

