

Osteosarcoma with Adenocarcinoma of Lung in Li-Fraumeni Syndrome: A Case Report

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Li-Fraumeni syndrome (LFS) is an autosomal dominant hereditary disorder characterised by a variety of different tumor types in children and young adults. That contains with a germline mutation in the tumor suppressor gene Tumor Protein p53 (TP53). That is extremely rare. Furthermore, this is sometimes overlooked. Here, we report a case of LFS which was confirmed by mutational analysis of the p53 gene. Also, literature review is intended to improve understanding of this disease entity.

Key words: Li-Fraumeni syndrome, hereditary tumor, osteosarcoma, family history

The most common primary malignant bone tumor, osteosarcoma, typically occurs in adolescents and young adults. Patients with localized osteosarcoma at presentation have a 60~80% rate of long-term survival. But carriers of a p53 germline mutation, Li-Fraumeni syndrome (LFS), have a life-time risk of 90% of developing a malignancy.¹⁾ LFS, which was first described in 1969 by Li and Fraumeni, is a cancer predisposition syndrome associated with sarcoma and wide spectrum of tumors.²⁾

Here, we report a p53 germline mutation in a 17-year-old girl LFS patient with osteosarcoma in proximal tibia and adenocarcinoma of lung.

that have heterogeneous signal intensity on T1-weighted and T2-weighted image on lateral metaphysis of the proximal tibia. The periosteal reaction and the extra-osseous formation were observed around the lateral cortex (Fig. 2).

Initially osteosarcoma was diagnosed and open bone biopsy was performed to confirm the pathologic diagnosis. Histopathologic examination of the biopsy specimen revealed an osteosarcoma, osteoblastic type. At the same time, we did diagnostic work-up to find the metastatic lesion by enhanced computed

Case Report

A 17-year-old girl was referred to our clinic because of pain in right knee on August 16, 2012. Physical examination revealed tenderness, mild heatness and swelling except limitation of the range of motion. Plain radiographs showed the 4 cm sized eccentric bone-destructive lesion with permeative pattern on right proximal tibia and the Codman's triangle on lateral cortex (Fig. 1).

On magnetic resonance imaging, there was 6×3 cm sized mass



Figure 1. Plain radiographs showed the 4 cm sized eccentric bone-destructive lesion with permeative pattern on right proximal tibia and the Codman's triangle on lateral cortex.

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Figure 2. On magnetic resonance imaging, there was 6×3 cm sized mass that have heterogenous signal intensity on T2-weighted (A) and T1-weighted image (B) GD (C) on lateral metaphysis of the proximal tibia. The periosteal reaction and the extraosseous formation was observed around the lateral cortex.

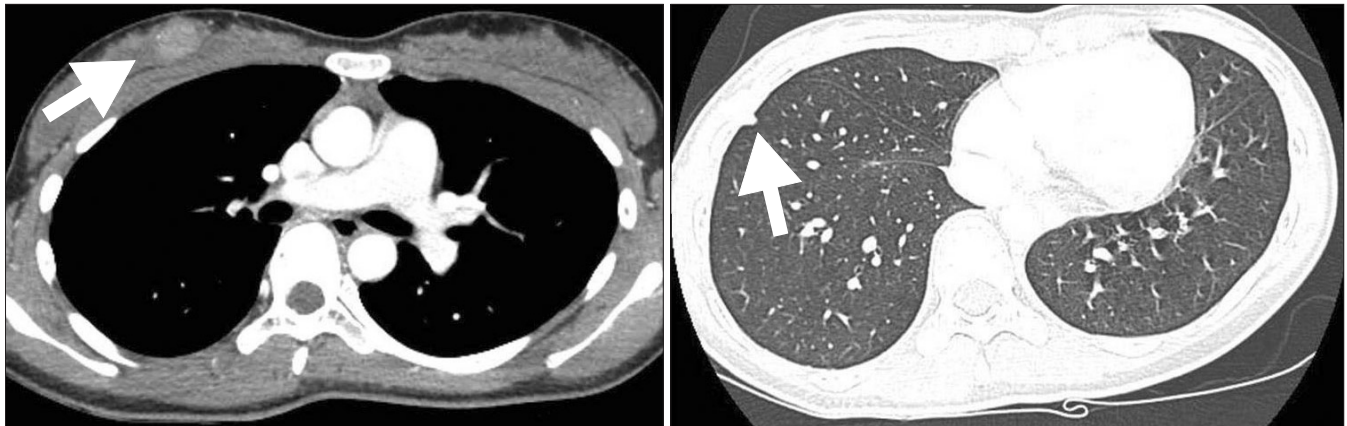


Figure 3. There are several small peripheral uncharacterized nodules in left lower lobe and right lower lobe of lung on enhanced chest CT.

tomography of chest and abdomen, whole body bone scan and positron emission tomography-computed tomography (PET-CT). And, we discovered 2 cm sized nodular lesion with contrast enhancement in right upper medial breast and several small peripheral uncharacterized nodules in left lower lobe and right lower lobe of lung on enhanced chest CT (Fig. 3) and same lesions on PET-CT (Fig. 4).

The patient referred to pediatric oncology department for preoperative chemotherapy. Then, excisional biopsy about the right breast nodule and video-assisted thoracoscopic operation about the right lower lobe nodule were performed. The right breast nodule was histopathologically confirmed to benign fibro-epithelial lesion, but the nodule of the right lung lower lobe was confirmed to adenocarcinoma in situ (bronchiole-alveolar carcinoma).

Through review of her family history revealed multiple early onset cancer, including colon cancer, gastric cancer, neuroendocrine cancer and breast cancer (Fig. 5). Her father has been diagnosed

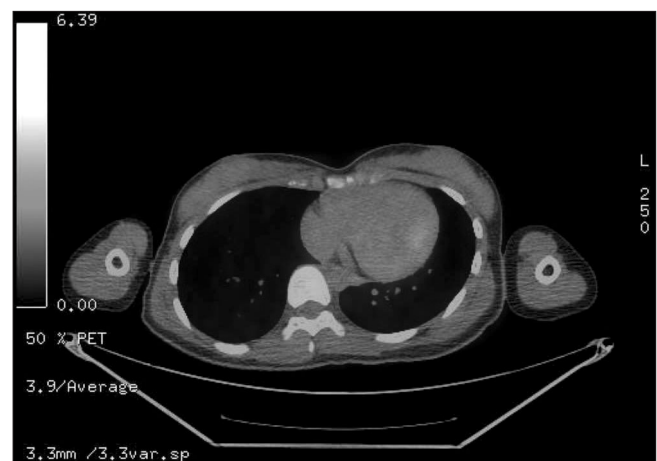


Figure 4. On PET-CT imaging, there are multiple nodules in both lobe of lung.

with gastric cancer at 40 years old and neuroendocrine cancer at 45 years old. And two uncles were died because of the colon cancer

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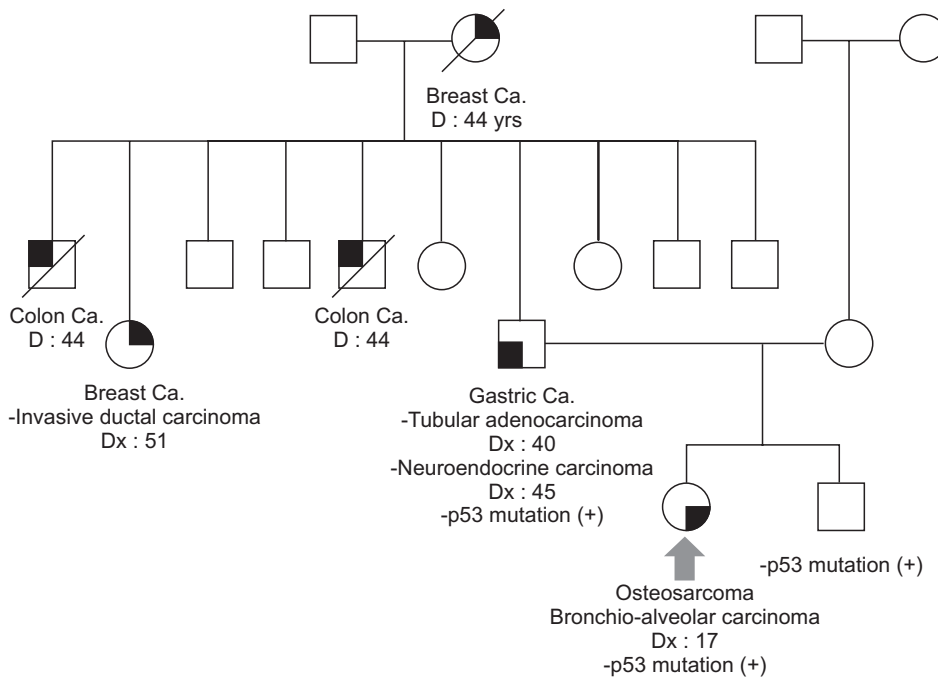


Figure 6. Wide marginal excision and tumor prosthesis reconstruction was performed. Post-operative 2 years, there is no radiologic abnormality change of the implant.

at 44 years old and 42 years old. Therefore, she was clinically diagnosed with LFS. So we performed genetic testing to evaluate the patient's susceptibility to LFS. Genetic analysis of the TP53 gene was performed using direct sequencing, revealed that the patient had a mutation in codon 175, resulting in an amino acid change from arginine to histidine.

After the planned preoperative chemotherapy, wide marginal excision and tumor prosthesis reconstruction was performed. Then,

she did exercise for range of motion of the knee. She had a postoperative chemotherapy with ifosfamide, carboplatin and etoposide. Post-operative 2 years, there is no radiologic abnormality change of the implant such as aseptic loosening etc. (Fig. 6).

Discussion

Li-Fraumeni syndrome (LFS) was described in 1969 by Li and Fraumeni²⁾ as an autosomal dominant hereditary disorder characterized by a variety of different tumor types in children and young adults. The most common forms of malignancies include breast cancer, soft tissue sarcomas, bone sarcomas, brain tumors, adrenal cortical carcinoma and leukemia. The diagnosis of LFS is based on strict clinical criteria. Germline mutations in the Tumor Protein p53 (TP53) gene are found in about 70% of families conforming to these criteria. However, there are many families with remarkable hereditary predisposition to cancer suggestive of LFS who do not meet the strict diagnostic criteria, and more relaxed criteria has been proposed for TP53 mutation testing, for example, the Li-Fraumeni like (LFL).

In other words, LFS is classified into two major subgroup: classic LFS and LFL syndrome, which share some, but not all, of the features of LFS.³⁾

Classic LFS was based on 24 families.⁴⁾ The classical definition of the LFS is based on the following three parameters: (1) a proband with a sarcoma diagnosed before the age of 45; (2) a first degree relative with cancer before the age of 45; and (3) another first or

second degree relative with either a sarcoma diagnosed at any age or any cancer diagnosed under the age of 45. Although sarcomas are quite frequently observed LFS, a broad range of other tumors may occur including breast cancer, brain tumors, lung cancer, laryngeal cancer, leukemia, adrenal cortical neoplasia, and others. Furthermore, more relaxed criteria were released for variations of a LFL syndrome.^{5,6)} More inclusive clinical classification schemes were described by Birch and Eeles⁷⁾ in 1995 to 1996, which characterized LFS but that did not fulfill the strict definition.^{7,8)} The classic LFS, Birch and Eeles criteria are generally used in clinical practice. So, this patient met the criteria for Classic LFS (Birch and Eeles). Naturally, germinal mutations in the p53 tumor suppressor gene account for the increased susceptibility to cancer in LFS.

Like this patient, osteosarcoma has been well characterized as one of the tumors known to occur in LFS, the cancer predisposition syndrome resulting from germline mutations in TP53. The TP53 protein functions mainly as a transcription factor, and is important for normal cell growth, apoptosis, and DNA repair. The TP53 gene has been observed to undergo somatic mutation in tumors, many of which disrupt the DNA-binding domain, and result in a loss of tumor suppressor function, leading to a more aggressive tumor phenotype.^{9,10)}

Like LFS the identification of at-risk family members by predictive testing is often recommended as enhanced surveillance for early diagnosis and prevention of disease is a critical part of primary care. Also, the risk of developing secondary, radiation-induced malignancies was described as elevated in LFS patients, since the first reports of LFS by Li and Fraumeni.¹⁾ So exposure should be as low as possible, although a general contraindication for any type of radiological diagnostic or treatment cannot be started.

In conclusion, LFS is a hereditary cancer syndrome characterized by a high risk of developing various types of cancer from birth through late adulthood, often at younger ages than normally expected. And most of the core cancers of LFS area associated with a poor

prognosis, so it is important to have regular check-ups and cancer screening test. In other words, cancer screening examinations are medical tests performed when a person has no symptoms. Likewise, if you find a tumor in young patients we should always keep in mind familial cancer syndrome like LFS.

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골육종과 폐선암을 동반한 리-프라우메니 증후군: 증례 보고

오창선 • 이진호* • 정성택 • 나보람
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Li-Fraumeni syndrome은 소아나 청장년층에서 다양한 형태의 종양을 유발할 수 있는 상염색체 우성 유전 질병이다. 이는 종양억제 유전자인 TP53의 변형에 의해 발생하게 된다. 이 질환은 매우 드물며, 진단되지 못하고 간과되는 경향이 많다. 이에 저자들은 17세, 폐선암을 동반한 근위 경골 골육종 환자에서 가족력을 통해 이 질환을 의심하고, 유전자 검사를 통하여 확진한 증례를 보고하고자 한다.

색인단어: 리-프라우메니 증후군, 유전성 종양, 골육종, 가족력

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