CASE REPORT

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Li-Fraumeni syndrome – a case report

Li-Fraumenijev sindrom

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Abstract

Introduction. Li-Fraumeni syndrome (LFS) is a hereditary familial predisposition to a wide range of certain, often rare malignant diseases. Patients also have an increased risk of developing secondary and even tertiary malignancies throughout their lifetime. The most common malignancies are soft-tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinoma, and acute leukemia. The syndrome is inherited as an autosomal dominant disorder. In most families with LFS, germline mutations of the tumor protein have been identified on the *TP53* gene. To our knowledge, this is the second case report of LFS that has been reported in our country so far. **Case report.** We present five members of the same family with malignant diseases typical for LFS. A woman at the age of 21 had recurrent astrocytoma and mediastinal liposarcoma. Her older sister had rhabdomyosarcoma and liver cancer and died at the age of 18. The mother of their father was diagnosed with breast cancer at the age of 45, and she died at the age of 52. The father's sister had osteosarcoma and died before the age of 40. The father was diagnosed with lung adenocarcinoma at the age of 49, two years after the death of his second daughter. Genetic analysis identified a pathogenic, heterozygous germline mutation of the *TP53* gene. He also has a third, 8-year-old daughter for whom he denied testing for LFS. **Conclusion.** Genetic analysis for LFS of all family members is required in patients with rare and multiple malignancies but also frequent and early onset malignancies in the family. Screening for the detection of early cancer manifestation is the key to prolonged survival in people with LFS.

Key words:
diagnosis; family; genetic diseases, inborn; li-fraumeni syndrome; mutation; serbia.

Apstrakt

Uvod. Li-Fraumenijev sindrom (LFS) je nasledna porodična predispozicija za širok spektar određenih, često retkih malignih bolesti. Bolesnici, takođe, imaju povećan rizik od razvoja sekundarnih, pa čak i tercijarnih malignih bolesti tokom čitavog života. Najčešći su sarkomi mekih tkiva i kostiju, karcinom dojke, tumori mozga, adrenokortikalni karcinom i akutna leukemija. Sindrom se nasleđuje kao autozomno dominantni poremećaj. U većini porodica sa LFS, identifikovane su heterozigotne mutacije na genu *TP53*. Po našem saznanju, ovo je drugi prikaz LFS u Srbiji. **Prikaz bolesnika.** Prikazujemo porodicu u kojoj su kod pet članova dijagnostikovane maligne bolesti tipične za LFS. Žena u 21. godini života lečena je zbog rekurentnog astrocitoma i medijastinalnog liposarkoma. Njena starija sestra imala je rabdomiosarkom i karcinom jetre i umrla je u 18. godini. Majci njihovog oca dijagnostikovan je karcinom dojke u 45. godini, a umrla je u 52. godini života. Očeva sestra imala je osteosarkom i umrla je pre 40. godine života. Njihovom ocu dijagnostikovan je adenokarcinom pluća u životnom dobu od 49 godina, dve godine nakon smrti druge ćerke. Genetičkom analizom otkrivena je heterozigotna mutacija gena *TP53*. On takođe ima i treću, osmogodišnju ćerku za koju nije odobrio genetičko testiranje. **Zaključak.** Kod bolesnika sa retkim i višestrukim malignim bolestima, kao i kod čestih i ranih maligniteta u porodici, potrebna je genetička analiza za LFS svih članova porodice. Ciljana provera prisustva ranih manifestacija malignih bolesti ključna je za otkrivanje LFS i produženo preživljavanje obolelih od ovog sindroma.

Ključne reči:
dijagnoza; porodica; genetičke bolesti, urođene; li-fraumeni sindrom; mutacija; srbija.

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Introduction

Li-Fraumeni syndrome (LFS) is a hereditary familial predisposition to a wide range of certain, often rare malignant diseases. To date, approximately 400 families with LFS have been reported in the literature [1]. The prevalence is 1–9 : 100,000 inhabitants [2]. The syndrome was first recognized in 1969 by Frederick Li and Joseph Fraumeni Jr while studying pediatric and familial malignant tumors at the National Cancer Institute. They described multiple malignant diseases in children and young adults in four families and increased risk for multiple primary tumors [3]. LFS patients also have an increased risk of developing secondary and even tertiary malignancies throughout their lifetime. The most common are soft-tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinoma, and acute leukemia [4]. The lifetime risk of malignant disease in individuals with LFS is ≥ 70% for men and ≥ 90% for women [5]. This predisposition syndrome is inherited as an autosomal dominant disorder. In most families with LFS, germline mutations of tumor protein p53 gene (*TP53*) have been identified in chromosome 17p13.1, which codes for a transcription factor implicated in cell proliferation, apoptosis, and genomic stability [6].

A diagnosis of LFS and performance of the *TP53* gene mutation testing is considered for anyone with a personal and family history that meet one out of the following three criteria [1]: 1) if a person is diagnosed with a tumor from the LFS tumor spectrum, before the age of 46, which includes any of the following diseases – soft-tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumor, adrenal cortical carcinoma, leukemia or lung cancer, and at least one first-degree or second-degree family member with an LFS-related tumor, except breast cancer which developed before the age of 56 or with multiple tumors; 2) if a person has multiple tumors, except multiple breast tumors, two of which belong to the LFS tumor spectrum and the first of which occurred before the age of 46; 3) if a person is diagnosed with adrenocortical carcinoma or a tumor in the choroid plexus, meaning a membrane around the brain, regardless of family history.

In addition, patients with anaplastic rhabdomyosarcoma, women with breast cancer prior to the age of 31, and patients with hypodiploid acute lymphoblastic leukemia and Sonic Hedgehog medulloblastoma should be tested, regardless of their family history [5,7].

Case report

Case 1

The proband was a woman at the age of 21. She was admitted in April 2016 to Neurology Department due to a headache that lasted for two months. She also reported occasional tingling in the left half of her face. She reported no history of loss of consciousness, convulsion, chronic diseases, or smoking. There was a family history of frequent malignancies. The mother of her father was diagnosed with breast cancer at the age of 45 and died at the age of 52. The father's sister was treated for osteosarcoma. She died before the age of 40. The proband's older sister had rhabdomyosarcoma and liver cancer and died at the age of 18. The family tree is shown in Figure 1. Case 1 is marked with an arrow.

Neurological examination found no significant discrepancies. The patient underwent diagnostic procedures. Blood analysis results, except for mild anemia, revealed normal findings. Electroencephalography found focal somatosensory seizures (Figure 2), and magnetic resonance imaging (MRI) showed an expansive change in the right parietal lobe of the brain (Figure 3).

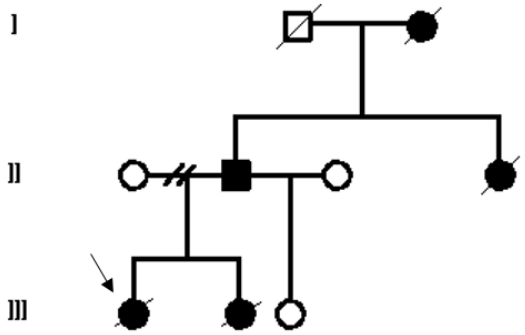

Fig. 1 – Family tree illustrating the presence of different malignant diseases in three generations. In the first generation, the father's mother had breast cancer and died at the age of 52. In the second generation, the father had lung adenocarcinoma; his sister had osteosarcoma and died at the age of 40. The third generation represents two daughters from the first marriage who had rhabdomyosarcoma, liver cancer, and astrocytoma and a third 8-year-old daughter from the second marriage, currently without cancer. Symbol of square – male; symbol of circle – female; affected person symbols are colored black; married or in partnership person symbols are connected with a horizontal line; divorced or separated person symbols are connected with a crossed horizontal line.

We concluded that the change in the parietal right lobe showed the characteristics of the expansive process. Neurosurgical treatment and histopathological (HP) verification of the change were performed. Astrocytoma anaplasticum (World Health Organisation – WHO, grade III) was diagnosed. Radiotherapy was performed in the optimal period, and the patient was controlled periodically until 2018. In April 2018, chest pain occurred, and a large mass in the upper mediastinum involving the superior vena cava was found on computed tomography (CT) (Figure 4). A surgical biopsy was performed, and the HP finding confirmed pleomorphic liposarcoma. A positron emission tomography can showed the dissemination of the tumor in the liver, pericardium, and skeletal system. Chemotherapy treatment was recommended. In June 2018, the patient was urgently admitted to the hospital due to severe headaches and signs of increased intracranial pressure. CT showed a recurrence of the brain tumor in the right parietal lobe. There were suspicious signs of bleeding in the tumor (Figure 5). An emergency craniotomy was performed. The

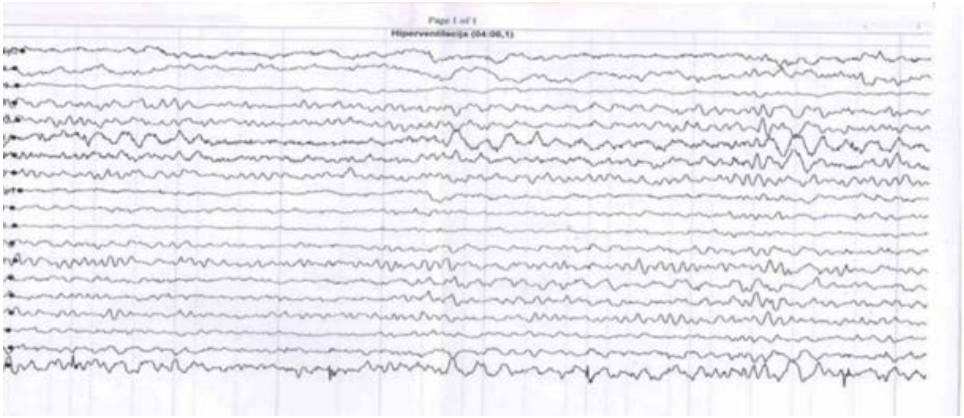

Fig. 2 – Electroencephalography finding shows focal somatosensory seizures.

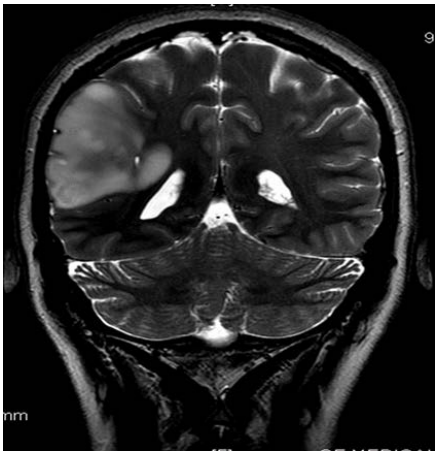

Fig. 3 – Head magnetic resonance imaging shows a tumor in the right parietal lobe of the brain.

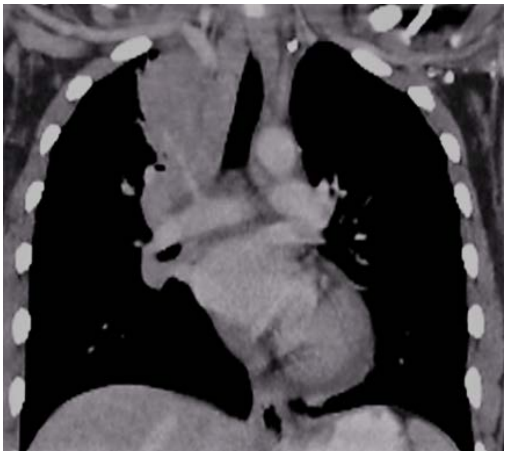

Fig. 4 – Chest computed tomography scan shows a tumor of the upper mediastinum involving the *superior vena cava.*

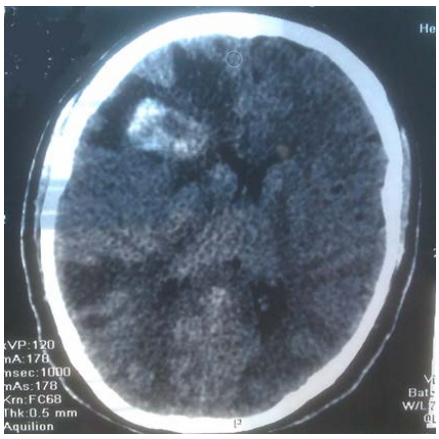

Fig. 5 – Head computed tomography scan shows recurrence of a brain tumor in the right parietal lobe with suspected bleeding.

tumor was extirpated and made external drainage of cerebrospinal fluid. HP finding confirmed recurrence of astrocytoma.

In the further course, there was no improvement in the patient's condition. The fatal outcome occurred in July 2018 at the age of 23.

Due to the existence of several rare malignant diseases in the family (grandmother, sister, and aunt), the LFS was suspected. The woman's father has been invited to genetic counseling several times but did not respond.

Case 2

The second case is the father of the first presented patient (Case 1). A man at the age of 49 was admitted to the Pulmonology Department due to cough and back pain in October 2020. In his history, he denied chronic diseases and smoking. His mother, two daughters (18 and 23 years), and a sister died of rare and multiple malignancies. He has a healthy 8-year-old daughter. Radiography and chest CT revealed a tumor in the left upper lung lobe, approximately 4 cm in diameter, with pleural effusion (Figures 6 and 7).

Due to back pain, radiography and skeletal scintigraphy were performed. Metastases were found in the spinal column. The bronchoscopy findings were normal. Pulmonary adenocarcinoma was confirmed from a transbronchial lung biopsy. Additional testing found epidermal growth factor receptor – EGFR mutation in exon 21 (L858R). The clinical stage was T2aN2M1c (bone metastases – OSs) – stage IVB. The oral administration of tyrosine kinase inhibitor – afatinib was started in November 2020. Palliative radiotherapy for metastatic disease in the spine was also applied in December 2020. On the last assessment in October 2021, there was a partial response according to Response Evaluation Criteria In Solid Tumors, version 1.1. (RECIST 1.1) (Figure 8). The patient was in good general condition with Eastern Cooperative Oncology Group (ECOG) performance status 1.

The patient was offered genetic testing which he accepted. Analysis of the *TP53* was performed by sequencing genomic DNA isolated from peripheral blood leukocytes. A pathogenic, heterozygous germline mutation *TP53* gene on exon 5, codon 151, CCC >ACC, c.451C >A (p.Pro151Thr) was identified. However, the patient did not give his consent for this test to be performed on his 8-year-old daughter.

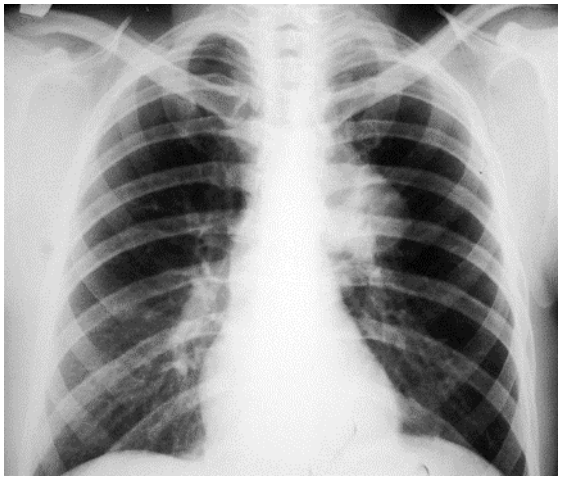

Fig. 6 – Chest radiography shows a tumor in the left lung.

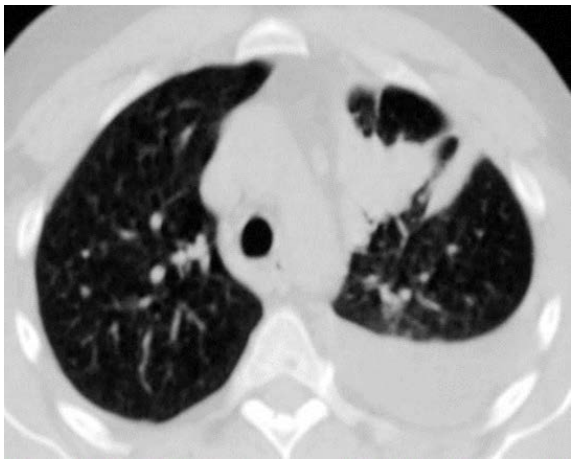

Fig. 7 – Chest computed tomography scan shows a tumor in the left lung with pleural effusion.

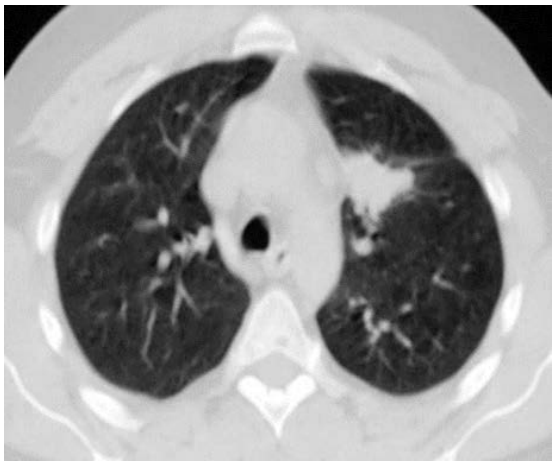

Fig. 8 – Chest computed tomography scan shows partial response to treatment.

Discussion

LFS is a rare autosomal-dominant inherited syndrome containing a germline mutation in the *TP53* gene, which predisposes to oncogenesis.

Furthermore, there is a hereditary condition of cancer predisposition that has been called LFS-like syndrome (LFL), which is defined as proband with any childhood cancer, adrenocortical tumor, brain tumor, or sarcoma in people under 45 years of age, the first or second-degree relative in the same lineage with LFS tumor at any age, and the first or second-degree relative in the same lineage with any type of malignancy before the age of 60 [8]. Approximately 70% of families affected by classical tumors carry germinal mutations in *TP53*. However, 40% of patients with LFL phenotype (families with other malignancies, different from classical tumors) carry *TP53* deleterious mutations. *TP53* mutations, associated with LFS or LFL, are mainly found in the DNA binding domain. Only a few cases of *TP53* mutations are out of this hotspot location [9, 10]. Looking into complete family history over multiple generations is very important as it could suggest an increased risk of cancer occurrence within a family. Likewise, it is equally important to regularly update the family history as the risk factor can change over the years. In our case, the mutation was found in the father who did not know about the *TP53* mutation until he was 49 years old. His variant of mutation is classified as likely pathogenic according to the ClinVar database [11]. The father was the only family member genotyped. His mother and two daughters probably had a mutation due to the early and rare cancers from which they died. The reported case describes the appearance of cancer at a young age, the presence of multiple malignancies in the same person, and the occurrence of rare malignancies within the same family. After the diagnosis of malignant disease, presented patients were classified and treated according to current oncology guidelines and recommendations [12–14]. Assessment of the effects of anticancer treatment was done according to Response Evaluation Criteria in Solid Tumors-RECIST 1.1 [15]. The performance status was assessed based on Eastern Cooperative Oncology Group-ECOG [16]. Despite the obvious connection between the reported patients, the diagnosis of LFS was made only after the confirmation of a malignant disease in the father. There were several reasons for this. First of all, LFS is rare, with an incidence of 1–9 : 100,000 inhabitants. The second reason was that all members of this family had malignancies of different primary sites and were treated in different medical institutions and countries. Moreover, the father probably did not pay enough attention to family history after two of his daughters were diagnosed with cancer. The third possible reason was the father's refusal of genetic testing for LFS even after his second daughter was diagnosed with two malignant diseases at an early.

Detection of *TP53* mutation in the third 8-year-old daughter could have led to inclusion in a screening program for early cancer detection which would significantly increase the possibility of longer survival. In our case, despite being made aware of this, the family did not agree to genetic testing for the third daughter. They believe that knowledge of the existence of LFS would create psychological pressure, which they are not ready to deal with. We hope the family will agree to genetic testing in the near future because early diagnosis leads to earlier and more effective treatment. This case also confirms both the need to provide patients with psychological support as well as information about the significance of regular diagnostic procedures in order to achieve the best possible outcome. These screening protocols recommend that carriers of the mutation should perform an abdominal ultrasound every 3–4 months, an annual MRI of the whole body, and an annual brain MRI (the first with gadolinium enhancement) from the first year of life. In addition, female carriers should perform an annual breast MRI from age 20. The possibility of a mastectomy that reduces the risk of cancer can be discussed, depending on the case [1]. However, a lot of current strategies using small molecule drugs to reactivate or modify dysfunctional *TP53* protein are being actively studied, but not yet in clinical trials with LFS patients [17].

Conclusion

Screening for the early manifestation of malignant disease is the key to prolonged survival in people with LFS. People with LFS require education about this genetic disorder, the types of malignancies they have an increased risk of, and the signs and symptoms of these diseases. Reproductive options for those in fertile age should be discussed. A periodic physical examination, recommended to be done annually, should be performed, including skin, breast, and neurological assessments. In the future, gene therapy will give optimism for the possibility of longer survival.

Conflict of interest

The authors declare no conflict of interest.

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