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 very rare familial disease with the predisposition to the development of malignant tumors, such as osteosarcoma, breast cancer, brain neoplasm, leukemia, and adrenal tumors. Inheritance is autosomal dominant and is caused by heterozygous mutations in the p53 gene. The diagnosis is based on clinical criteria: a person under the age of 45 years suffering from sarcoma, the closest relative younger than 45 years diagnosed with cancer and a relative of the first or second degree, which is up to 45 years, was diagnosed with cancer and was diagnosed with sarcoma at any age. **Case report.** The presented family with three members diagnosed with malignant disease typical for LFS suggests the need to carefully follow those diagnosed with LFS related tumor. A 24-year-old man diagnosed and treated for osteosarcoma of the maxilla died in the first year. His younger brother was submitted to surgery due to osteosarcoma of the mandible three years later, and a year later in his 24 year he had no signs of locoregional recurrence. Their mother was operated in 1996 for glioblastoma multiform brain cancer and ductal carcinoma, and died two years later at the age of 33. **Conclusion.** The presented family highlights the need for careful examination, inspection and notification of the risks of family members diagnosed with LFS related tumors.

Key words:
li-fraumeni syndrome; diagnosis; treatment outcome; prognosis.

Apstrakt

Uvod. Li-Fraumenijev sindrom (LFS) predstavlja veoma retko familijarno obolenje sa predispozicijom za razvoj pojedinih malignih tumora, kao što su: osteosarkom, karcinom dojke, neoplazma mozga, leukemija i adrenalni tumori Nasleđuje se autozomno dominantno, a nastaje usled heterozigotne mutacije na genu p53. Dijagnoza se postavlja na osnovu kliničkih kriterijuma: osoba mlađa od 45 godina obolela od sarkoma, najbliži srodnik mlađi od 45 godina oboleo od karcinoma i srodnik prvog ili drugog kolena koji je do 45. godine oboleo od karcinoma ili oboleo od sarkoma u bilo kom uzrastu. **Prikaz bolesnika.** U radu je prikazana porodica u kojoj su kod tri člana dijagnostikovana maligna obolenja karakteristična za LFS. Muškarac star 24 godine oboleo i lečen od osteosarkoma gornje vilice preminuo je u toku prve godine. Njegov mlađi brat je 3 godine kasnije operisan od osteosarkoma donje vilice, a godinu dana kasnije u svojoj 24 godini bio je bez znakova lokoregionalnog recidiva. Njihova majka je 1996. godine operisana od multiformnog glioblastoma mozga i duktalnog karcinoma dojke. Umrla je dve godine kasnije u 33. godini života. **Zaključak.** Ovaj prikaz ukazuje na potrebu pažljivog pregleda, kontrolisanja i obaveštavanja o rizicima članova porodice obolelih od tumora koji su u vezi sa LFS.

Ključne reči:
li-fraumeni sindrom; diagnosis; lečenje, ishod; prognoza.

Introduction

Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome caused by heterozygous mutation in the p53. This syndrome is very rare with ~ 400 families reported in the literature. This syndrome is characterized by autosomal dominant inheritance and early appearance of tumors, multiple tumors within a person, and multiple affected family members [1]. Osteosarcoma, soft tissue sarcoma, leukemia, brain cancer, breast cancer, and adrenal cortical tumors are the most common types of cancer found in LFS families. This syndrome is also known as sarcoma, breast, leukaemia and adrenal gland (SBLA) syndrome [2].

Classic LFS syndrome is defined as proband with a sarcoma under the age of 45 and the first-degree relative (sibling, parent, or child) with any cancer diagnosed before the

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age of 45, and the first- or second-degree relative (grandparent, uncle, aunt, nephew, niece, or grandchild) diagnosed with any cancer before the age of 45 or with sarcoma diagnosed at any age [3].

There is also a hereditary condition of cancer predisposition that has been called Li-Fraumeni-like syndrome (LFL) which is defined as proband with any childhood cancer, or a sarcoma, adrenocortical tumor, or brain tumor before the age of 45, 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 cancer before the age of 60 [4].

LFS and LFL are genetic conditions. Approximately 70% of LFS cases and 40% of LFL cases contain germline mutations in the p53 gene on chromosome 17p13.1 [5]. TP53 mutations have been primarily implicated in Li–Fraumeni syndrome [6]. Mutations in another gene, called CHEK2, have been found in another form of Li-Fraumeni syndrome (LFS2). Women with CHECK2 mutations could be in increased risk for breast cancer [6]. A third locus has been mapped on the long arm of chromosome 1 (1q23) but the gene has not been identified.

Case report

We presented a family with three members diagnosed with a malignant disease typical for LFS, so that the clinical criteria for LFS were met.

A proband with sarcoma before the age of 45-elder son with osteosarcoma died at the age of 24

A 24-year-old man with swelling in the region of upper incisors observed in January 2008, visited maxillofacial surgeon in May 2008. Local extraoral finding showed swelling of premaxilla with a lobular tumor dimension 30 × 20 × 10 mm in the oral premaxilla region which partially covered the cheek surface of the upper central incisors, but the mucosa over the tumor was preserved and seemed unchanged (Figure 1). Left

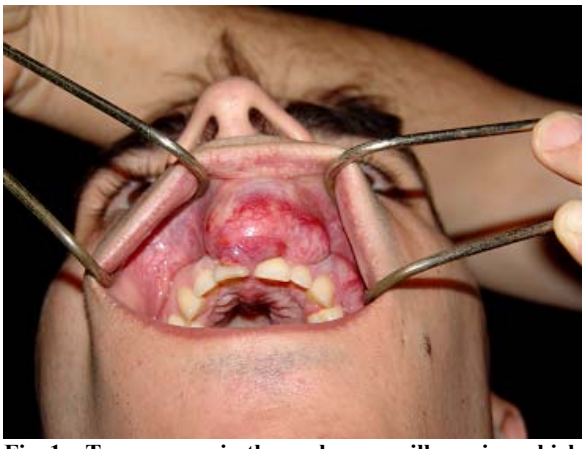

Fig. 1 – Tumor mass in the oral premaxilla region which partially covered the cheek surface of the upper central incisors in the elder son-proband.

maxillary alveolar process was completely ballooned. Pathology of biopsy indicated a chondrosarcoma. CT scan showed the sclerotic, osteolytic areas with inhomogeneous and prominent periosteal reaction in the alveolar process of the left maxilla and the lower part of the left maxillary sinus was filled with tumor mass that infiltrated the lower nasal concha. The neck had no of enlarged lymph nodes.

In early June 2008 the patient underwent total maxillectomy which included a resection of the premaxilla until the contralateral (right) first premolar and resection of the lower nasal concha. Histological findings showed an osteosarcoma with small cells with some fibroblastic and chondroblastic foci (Figure 2).

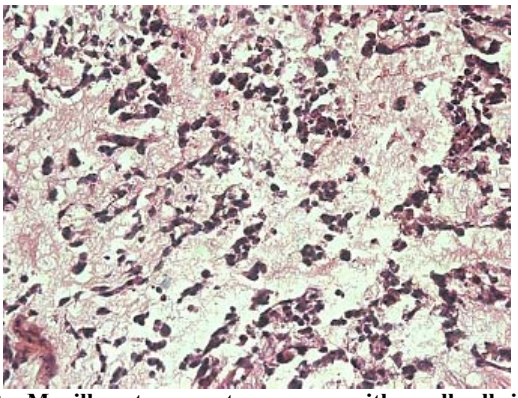

Fig. 2 – Maxillary tumor osteosarcoma with small cells in the myxoid stroma in the elder son-proband (HE, ×200).

The radiotherapy started in the optimal period, but only a month after maxillectomy a recurrence in the midline of the nasal cavity was diagnosed. A resection of the tumor was followed, and the finishing of previously established radiotherapy. In the coming months there was a locoregional recurrence – sphenoid bone infiltration and left orbital tumor progression leading to blindness. Distant metastases in the lungs and multiple secondary cutaneous deposits occurred. The death was due to cardiopulmonary failure in December 2008. Subsequent histological analysis indicated high grade conventional osteosarcoma chondro and osteoblastic types.

A first-degree relative diagnosed with any cancer before the age of 45 – mother with breast and brain cancer died at the age of 33

From the data of the previous two patients found out that their mother was born in 1965 underwent separately brain and breast surgery in 1996. Pathohystological findings showed invasive ductal carcinoma of breast and brain multiform glioblastoma (Figure 3). She died in 1998. She had no siblings.

A first-degree or second-degree relative diagnosed with any cancer before the age of 45 or diagnosed with sarcoma at any age – younger son with osteosarcoma diagnosed at age of 23

A 23-year male observed a sweling and deformity of the left mandible in April 2012 (Figure 4). Two months before he noticed a numbness of the lower lip. Maxillofacial surgeon examined him and endosseous biopsy was performed a few days later. Pathology findings indicated a ma-

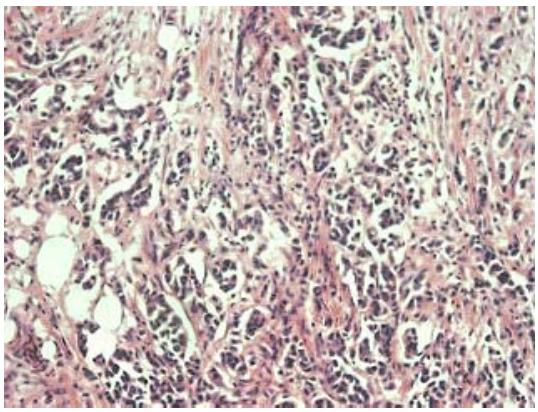

Fig. 3 – Ductal infiltrative breast carcinoma in the mother (HE, ×200).

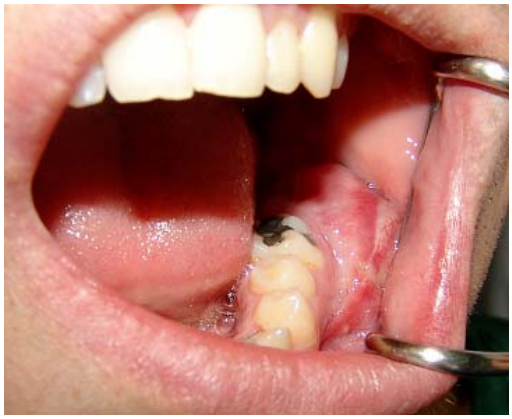

Fig. 4 – Deformity of the left mandible in the younger son.

lignant mesenchymal tumor, probably chondrosarcoma. The radiologist on computed tomography (CT) scanning described extended body of the mandible from the mental foramen to the left lower jaw angle. The medulla was modified by a bone mass characterized with inhomogeneous higher attenuation and cortex showed individual partial erosion. In the neck region II were present lymph nodes greatest diameter 17 mm, oval.

In the beginning of June, he underwent hemimandibulectomy with supraomohyoid neck dissection. Histological findings were: osteosarcoma with fibroblastic and chondroblastic foci (Figure 5). Immunohistochemical characteristics

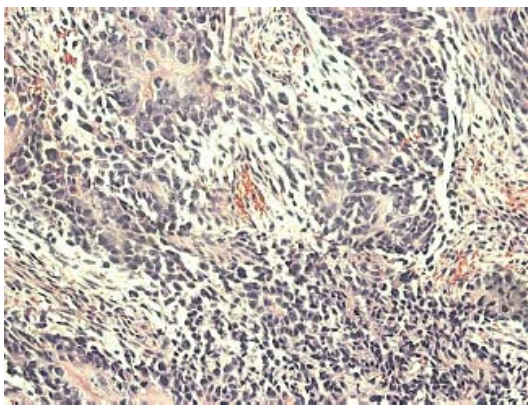

Fig. 5 – Mandibular osteosarcoma with the small round cells surrounding homogenous eosinophylic osteoid deposits with some fibroblastic cells in the younger son (HE, ×200).

of tumor cells were: vimentin and S-100 and CD99 positive, and negative on CD79a, CD3, HMB45, desmin, MyoD1, EMA, CK18, CK5/6. The proliferative index (Ki67) was rather uneven and very high, on the average 30% of cells. The neck was tumorfree.

A combined chemo- and radiotherapy followed. The patient was regularly controlled clinically and by imaging magnetic resonance imaging (MRI) of the head, chest CT, abdominal ultrasound (US). Locoregional recurrence and distant metastases were not registered. He regularly performed his profesional and daily activities.

Discussion

Li–Fraumeni syndrome is named in honor of Frederick Pei Li and Joseph F. Fraumeni, Jr. [7], the American physicians who first recognized and described the syndrome. In the study on 648 childhood rhabdomyosarcoma patients, they identified 4 families in which siblings or cousins had a childhood sarcoma. These 4 families also had distinct histories of breast cancer and other neoplasm, assuming a new familial cancer syndrome of different tumors. The following prospective study confirmed the high risk of different tumors in family members [8]. In contrast to other hereditary cancer syndromes, which are mainly characterized by site-specific cancers, LFS presents a diverse of tumor types. The most common types are soft tissue sarcomas and osteosarcomas, breast cancer, leukemia, and adrenocortical carcinoma.

Pearson et al. [9] reported 2 families with LFS. In the first, the mother had breast cancer and 3 of her 4 children had adrenocortical carcinoma, rhabdomyosarcoma, and medulloblastoma; in the other, the mother had breast cancer and 2 of her 3 children had rhabdomyosarcoma and adrenocortical carcinoma. An increased risk for melanoma [10], Wilms' tumor, and cancers of gaster, esophagus, colon, pancreas, gonadal germ cells and lung, have also been reported [11–13]. Someone who has LFS may be at risk for neoplasm of almost every part of the body.

The syndrome is characterised by the appearance of tumors associated to LFS at an early age [14] and the occurrence of multiple primary malignant tumors [1, 14]. Tumors in the case of family were diagnosed in 30, 24 and 23 years of age. The mother was diagnosed by multiple primary malignance – of the brain and the breast, during one calendar year. The median age of breast cancer diagnosis in LFS woman is 33 years average and 16 years of brain tumor onset [15]. Determination of TP53 gene mutation is not as high-sensitivity method; it is positive in 50–70% of cases. LFS is a very rare disease, so we suspected on this one when the younger brother was diseased. The same surgeon operated both of brothers and set of the clinical diagnosis of LFS.

The early diagnosis of LFS raises the issue of preventive screening for carriers of mutations that can have long-term risk of development of malignancy, which is estimated at 73% for men and 100% for women carriers [16]. Malignant brain tumors and breast cancer are particularly common in older TP 53 mutation carriers, requiring full annual clinical examination and regular screening for breast cancer for females. A high de-

gree of suspicion should be maintained for LFS carriers who complain of unexplained persisting symptoms.

Conclusion

The case of families with Li-Fraumeni Syndrome indicates the need of getting a detailed family history in patients with tumors associated with this syndrome. Mutations in the TP53 gene do not prove a specific finding for Li-Fraumeni Syndrome which is the reason for the annual clinical review and full physial examination with regular screening for breast cancer for females. Informing family members about the possible risks related to Li-Fraumeni Syndrome could lead to the early detection of Li-Fraumeni Syndrome related tumors.

R E F E R E N C E S

1. *Hisada M, Garber JE, Fung CY, Fraumeni JF, Li FP.* Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998; 90(8): 606−11.
2. *Lynch HT, Guirgis HA.* Childhood cancer and the SBLA syndrome. Med Hypotheses 1979; 5(1): 15−22.
3. *Li FP, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA,* et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988; 48(18): 5358−62.
4. *Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM,* et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994; 54(5): 1298−304.
5. *Bachinski LL, Olufemi S, Zhou X, Wu C, Yip L, Shete S,* et al. Genetic mapping of a third Li-Fraumeni syndrome predisposition locus to human chromosome 1q23. Cancer Res 2005; 65(2): 427−31.
6. *Malkin D.* Li-Fraumeni syndrome. Genes Cancer 2011; 2(4): 475−84.
7. *Li FP, Fraumeni JF.* Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome. Ann Intern Med 1969; 71(4): 747−52.
8. *Li FP, Fraumeni JF.* Prospective study of a family cancer syndrome. JAMA 1982; 247(19): 2692−4.
9. *Pearson AD, Craft AW, Ratcliffe JM, Birch JM, Morris-Jones P, Roberts DF.* Two families with the Li-Fraumeni cancer family syndrome. J Med Genet 1982; 19(5): 362−5.
10. *Hartley AL, Birch JM, Marsden HB, Harris M.* Malignant melanoma in families of children with osteosarcoma, chondrosarcoma, and adrenal cortical carcinoma. J Med Genet 1987; 24(11): 664−8.
11. *Strong LC, Stine M, Norsted TL.* Cancer in survivors of childhood soft tissue sarcoma and their relatives. J Natl Cancer Inst 1987; 79(6): 1213−20.
12. *Li FP, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA,* et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988; 48(18): 5358−62.
13. *Masciari S, Dewanwala A, Stoffel EM, Lauwers GY, Zheng H, Achatz MI,* et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med 2011; 13(7): 651−7.
14. *Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ,* et al. Beyond Li-Fraumeni syndrome: Clinical characteristics of families with p53 germline mutations. J Clin Oncol 2009; 27(8): 1250−6.
15. *Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P,* et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res 2003; 63(20): 6643−50.
16. *Chompret A, Brugières L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A,* et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer 2000; 82(12): 1932−7.

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