Two Clinical Cases of Li-Fraumeni Syndrome and Prostate Cancer: Genetic Counseling and Clinical-Surgical Management

1. Introduction

Li-Fraumeni syndrome (LFS) is a genetic disease with autosomal dominant transmission that is associated with an increased predisposition to certain cancers. It is caused by a germline mutation of the TP53 tumor suppressor gene[1].

Tumors **classically** described in this syndrome are mainly bone and soft tissue sarcomas, as well as breast **cancer,** adrenocortical carcinomas, tumors of the central nervous system **and leukemias**. **However, a higher incidence of other neoplasms has been seen in LFS patients too** [2,3]. At the urological level, prostate **cancer** has also been observed in these patients [1-4], **and several recent publications also describe a greater predisposition of patients with TP53 germline mutations to suffer more aggressive prostate cancer** [5].

Health practitioners must be alerted to the presence of a hereditary syndrome in patients with early-onset cancer, as well as in the event of a family history involving multiple cancers. **Classical criteria to identify patients and families at risk of suffering from LFS have been described, followed by more permissive ones (Chompret, Eales/Birch)** [6-10]. In order to achieve early detection of potentially life-threatening diseases, genetic counseling is recommended for both patients and their relatives [4].

Prostate cancer is one of the most frequent neoplasms worldwide, and is the second most frequent in men [11]. However, it has not been recognized as one of the main neoplasms associated with LFS, so its diagnosis is not included in LFS screening programs [4,12].

In this paper we describe two clinical cases of patients with LFS and prostate cancer, and discuss the indications for genetic counseling. We highlight the implications of the syndrome for the management and follow-up of patients with prostate cancer.

2. Clinical cases

Case 1 (Figure 1-3)

A 45-year-old man **with a history of rhabdomyosarcoma at age 42, subsequently** diagnosed with LFS **upon detecting the Q144X mutation of the TP53 gene in a blood sample by means of gene sequencing using the Sanger method [TP53(NM_000546.6):c.430C>T(p.Gln144Ter)]**,

who enters a screening program due to high cancer risk. **The patient met LFS clinical criteria to request the genetic study** because he had a family history of tumors related to TP53 germline mutation. His father had died of stomach cancer at the age of 40, a twin brother died at the age of 3 due to an adrenal tumor, a living sister underwent bilateral mastectomy for breast cancer **at age 38**, a son died of a brain tumor at the age of 2, and a nephew died of leukemia at the age of 5. After a normal colonoscopy and gastroscopy, a full-body MRI showed pathological adenopathy in the right common iliac region and another in the external iliac region on the same side, **with no other pelvic abnormalities**. After performing the diagnostic tests, the patient presented with **obstructive** urinary tract symptoms. Laboratory tests showed a PSA of 122 ng/mL. Digital rectal examination identified a fixed, hard prostate with well-defined limits. A prostate biopsy revealed adenocarcinoma in the 14 extracted cylinders: ISUP grade 5 in six cylinders, ISUP 4 in four, ISUP 3 in two and ISUP 2 also in two, in addition to presenting a germline TP53 tumor suppressor gene mutation in **heterozygosis**. In view of the classification as high-risk adenocarcinoma, an extension study was performed using computed tomography and bone scintigraphy. Bone scintigraphy showed increased bone lesions at the level of the right pubis, left ischiopubic ramus, right sacroiliac joint, and left sacroiliac joint, all suggestive of metastasis. With the diagnosis of metastatic hormone-sensitive prostate cancer (HSCC1b), treatment was started with androgen deprivation therapy (ADT) + abiraterone acetate + prednisone as proposed by the LATITUDE trial. The patient began clinical follow-up and periodic imaging tests, and remained stable for 16 months until the appearance of new bone lesions in a control scintigraphy. He was diagnosed with castration-resistant prostate cancer. After discussing the case in the genitourinary tumor committee, it was decided to start treatment with docetaxel. After a complete response at 12 months, the patient presented biochemical and clinical progression with bone pain. Currently the patient is enrolled on a clinical trial in which he will receive anti-PD-1 immunotherapy with pembrolizumab.

Case 2

A 46-year-old patient followed up by multiple hospital units for suspected hereditary cancer syndrome. His oncological history included a left maxillary osteosarcoma **at age 26**, treated surgically with subsequent local radiotherapy, a pterygoid leiomyosarcoma **operated at age 38** followed by a combination of chemo-radiotherapy, a myelodysplastic **syndrome (MDS) at age 44 in complete remission** under hematological control, and multiple basal cell carcinomas in the epidermis.

His family history presented a deceased father at age 35 of soft-tissue sarcoma without genetic study, with no other history of interest and with two healthy children without relevant diseases.

After diagnosis of MDS and meeting the Chompret criteria for LFS, a genetic study was carried out using **next generation sequencing (NGS)** with a sample of peripheral blood and another one of fibroblasts from a skin biopsy. **TP53 gene sequencing confirmed** a substitution of a C>T base in heterozygosis at position 844 (c.844C>T) in exon 8 of the TP53 gene **using the**

Sanger sequencing method. This mutation causes an amino acid change in codon 282 **[TP53(NM_000546.6):c.844C>T(p.Arg282Trp)]**, which finally confirmed LFS diagnosis**.**

During **MDS** follow-up, the Department of Urology was contacted due to high PSA levels (5.23 ng/ml). Following the protocol, multiparametric magnetic resonance imaging of the prostate was performed, which identified two nodules in the transitional zone and left peripheral zone that were compatible with PIRADS-V. Prostate biopsy was indicated, showing tumor involvement with prostate acinar adenocarcinoma in nine cylinders (one right and eight left) with ISUP 5 in seven, ISUP 4 in one and ISUP 1 in one**. However, no somatic genetic study of the TP53 gene was performed**. After the extension study, no lesions suspicious of metastasis were observed on either the thoracoabdominopelvic computed tomography or the bone scan, and so it was decided to perform radical prostatectomy and pelvic lymphadenectomy.

Analysis of the specimen confirmed the results of the prostate biopsy (adenocarcinoma, ISUP 5, pT2), as well as metastatic involvement in a regional lymph node (N1). In August 2018, after discussing the case with a multidisciplinary committee, it was decided to refer the case for adjuvant radiotherapy associated with androgen suppression therapy, in view of the presence of locally advanced disease. After completing the combination treatment in February 2020, the patient presented undetectable levels of PSA in the control tests, with good urological evolution. During follow-up, he was admitted to the hematology unit due to progression of myelodysplastic syndrome associated with myelofibrosis. Magnetic resonance imaging revealed lesions in the liver and lungs suggestive of metastasis, which on biopsy turned out to contain cancer cells from the leiomyosarcoma treated in 2017. Finally, after progression of the cancer, the patient was admitted to the home hospitalization unit for palliative treatment, and died of multi-organ failure.

3. Discussion

Li-Fraumeni syndrome is classically considered a hereditary cancer predisposition syndrome with high penetrance. Various studies have reported that the risk of cancer of any type during the patient's lifetime can reach 70% in men and up to 90% in women [1,2]. The age groups most frequently affected are 16 - 50 years (with a cancer risk of 51%) and 51 - 80 years (cancer risk of 27%). The majority of patients diagnosed with prostate cancer are within **the latter** age range [4].

This syndrome has typically been related to an increased predisposition to a characteristic spectrum of cancers, most commonly breast cancers and bone or soft tissue sarcomas. These lesions tend to appear at an early age, generally during the first 45 years of life. **However, some studies have identified patients with specific mutations in the TP53 gene that only cause an attenuated/hypomorphic variant of the syndrome, suggesting a higher chance of survival in these patients and, therefore, HIGH risk of suffering neoplasms more associated with elderly people, such as prostate cancer [11].**

In the first clinical case, we can objectify a patient with a <u>family history of abundant neoplasms</u>. By applying <u>the LFS suspicion criteria, it can be seen</u> that this patient meets both the classic criteria (proband with soft tissue sarcoma at 42, brother who died of adrenal tumor at 3 years old and sister with multiple previous breast cancers at 45 years, among others) as well as the modified Chompret, Eales and Birch ones[6-10] . In this case, the genetic study was carried out both in the patient and in several members of his family, confirming a mutation of the TP53 gene (graphic 1). In this situation, it can be stated that the involvement of a hereditary genetic syndrome should be suspected in patients with a family history of multiple tumors within the characteristic spectrum of a syndromic pathology, as is the first case reported here.

Regarding the second case, it describes a patient with a personal history of many cancers, including tumors of the LFS spectrum. If personal and family history is analyzed, it is possible to identify compliance with the Chompret criteria [7-8] (multiple tumors, >2 within the LFS spectrum), so genetic study of both peripheral blood and cultured fibroblasts from skin biopsy was carried out, confirming pathological mutation of the TP53 gene. In the presence of multiple tumors in a patient, health practitioners dealing with uro-oncological pathologies should consider whether the patient is a carrier of a mutation that may cause a hereditary syndrome.

It is interesting to observe the different ways where the appearance of a genetic syndrome should be suspected. Therefore, it is essential to inquire about oncological antecedents both in the personal and family history, in order to detect a potential hereditary syndrome early. Such a diagnosis could subsequently modify the therapeutic options offered to the patient and could have prognostic implications in the natural history of the disease.

The diagnostic management of these patients should be optimized with specific tests and a genetic study of both the patient and their close relatives to establish the presence or absence of syndromic pathology, since early detection improves the discovery of new tumors and thus increases patient survival [1,4].

Genetic counseling is especially important in cases with suspected LFS. It must be carried out by an experienced multidisciplinary team, and consists of an initial interview with an exhaustive analysis of the patient's personal medical and surgical history in order to detect pathologies that might suggest a genetic syndrome. In addition, a detailed family tree chart of the patient should be constructed, and information on the genetic tests to be performed, occurrence and recurrence rates and on the risks and benefits of the genetic study should be provided [13,14].

Definitive diagnosis of LFS is made by genetic analysis showing characteristic pathological mutations in the TP53 gene. One of the challenges that the clinician faces is to establish when to refer a patient and his relatives for a genetic study in order to screen for cancer-related syndromes such as LFS.

Currently, in order to be eligible for a TP53 genetic study, a patient has to comply with the Chompret, Eales or Birch criteria, which are more lax than the classic criteria (which <u>would certainly leave out part of the population</u> at risk)[1,3].

In LFS, causative mutations are found in the germline, basically affecting the *TP53* gene. Most of them comprise missense mutations, which consist of the substitution of one nucleotide for another [15]. In order to identify genetic alterations in the TP53 gene, single-gene DNA sequencing and/or gene-targeted deletion/duplication analysis can be used [16].

In *TP53* gene analysis most mutations are found in exons 5-8, but clinical studies suggest that up to 13.6% of mutations may be missed if only these exons are analyzed. Therefore, the recommendation is to carry out an exhaustive search of the entire coding region of TP53 between exons 1-10 and the introns that flank these exons [16]. Databases documenting the mutations detected in patients with LFS are useful when evaluating patients and their families in genetic counseling [17].

Previous work has shown that germline mutations in genes such as *CHECK2* are related to the regulation of p53 and DNA repair, and may be associated with wild-type LFS. This increases the risk of different types of cancer, including prostate cancer [18]. In addition, recent genomic analyses performed in patients with adenocarcinoma of the prostate gland show a high prevalence of genetic defects in the signaling pathways of the *TP53* tumor suppressor gene, suggesting that this tumor may also play a key role in patients with LFS [19].

As seen previously, germline *TP53* mutations confer greater clinical aggressiveness to prostate cancer[5,20], although these results should be reproduced by further studies. Even so, other widely studied germline mutations (such as *BRCA2*) have been identified, which are associated with a higher rate of progression to metastatic disease and a worse general prognosis [21-23], (IS THERE A CONTROVERSY IN THIS FACT?) so it would be reasonable to think that this association probably also exists in carriers of TP53 germline mutations (¿¿¿???PREGUNTAR A MIGUEL¿¿¿¿?????).

Even though the link between LFS and prostate cancer has been previously reported[5], prostate cancer is not among the cancers most frequently associated with the syndrome, so no recommendations have been made regarding its screening[1]. However, some authors empirically recommend starting the diagnostic screening program for prostate cancer even before the age of 40. If diagnosis is confirmed, aggressive treatment should be initiated and the patient ought to be classified as high-risk according to the D'Amico classification[12].

Surgical treatment with radical prostatectomy (regardless of the approach used) is one of the best curative options for localized tumors – and also for locally advanced ones – in patients with life expectancy higher than 10 years[24]. It should be the first treatment option for management in patients with LFS.

External beam radiotherapy or brachytherapy are also valid options and are equivalent to surgery for definitive treatment [24]. However, previous studies have observed an increased rate of resistance to radiation in patients with mutations in the *TP53* tumor suppressor gene, causing an increase in DNA repair and greater cellular tolerance to DNA damage, all of which entails a lower rate of apoptosis [25,26]. In addition, an higher rate of tumors secondary to ionizing radiation has also been described in LFS patients, so the use of diagnostic and therapeutic procedures involving different types of radiation with ionizing energy should be kept to a minimum [1]. **Regarding this, in case 2 the multidisciplinary committee decided to**

apply adjuvant treatment with RT to the patient due to the clinical characteristics of his prostate cancer. Currently, a more conservative strategy could have been proposed, using periodic PSA testing until biochemical recurrence is suspected, thus delaying the use of radiotherapy. This alternative treatment strategy could have had an impact on the prognosis of the patient's myelodysplastic syndrome.

Chemotherapy can be administered as a scheduled treatment in metastatic prostate cancer, in combination with hormone therapy [24]. However, some cytotoxic agents are associated with an increased risk of secondary appearance of cancer such as leukemia, and this risk is greater in patients with LFS [1,27]. In addition, *TP53* mutations confer chemoresistance to some drugs such as docetaxel, so the use of taxane therapies as the first therapeutic option in these patients is not supported by the current evidence [28].

There is no clear evidence regarding the safety and benefit of the use of hormonal therapy (both the classic ADT and new antiandrogen treatments such as abiraterone acetate, enzalutamide and apalutamide) in LFS patients with metastasis. Studies should be carried out in patients with advanced stages of the disease who require hormonal therapy and are carriers of a *TP53* mutation. However, given the rarity of LFS, it is difficult to propose new studies capable of testing the current hypotheses.

Finally, in patients with a pathological mutation of the *TP53* gene, or in patients with a high risk of harboring the mutation (for instance, those with a relative affected by LFS), an exhaustive follow-up program should be carried out to ensure prompt detection of tumors in order to offer curative treatment [29]

As mentioned above, at present there is no follow-up and screening program for prostate cancer in patients with LFS. However, some clinical groups do initiate follow-up early, before the age of 40, and perform regular PSA measurements, **while other groups strongly recommend including prostate cancer in the LFS screening program** [5,12].

As for patients with prostate cancer under follow-up, it would be interesting to consider reducing tests involving ionizing radiation to minimize its impact on the development of other secondary neoplasms. Instead, follow-up with alternative techniques to tomography should be considered, such as serial magnetic resonance imaging [5].

4. Conclusions

Li-Fraumeni syndrome is a rare hereditary disease that is associated with an increased rate of certain characteristic cancers, including prostate cancer. Historically, prostate cancer has only rarely been associated with the syndrome, but recent analysis suggests that it may also be related to germline *TP53* gene mutations.

In LFS patients, early diagnostic management of prostate cancer is recommended. Screening should start before the age of 40 and aggressive treatment should be applied due to the nature of the disease. The preferred therapeutic option is surgery, since prostate cancer shows high rates of resistance to radiotherapy and to certain cytotoxic agents, as well as increased risk of secondary tumors.

The effectiveness of hormone therapy in LFS is uncertain due to the lack of current evidence.

5. Bibliography

1. Schneider K, Zelley K, Nichols KE, Garber J. Li-Fraumeni Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1999.

2. **Mai PL, Best AF, Peters JA, DeCastro R, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation-carriers in the NCI LFS cohort. Cancer. 1st december 2016;122(23):3673-81.**

3. **Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. January 2018;30(1):23-9.**

4. Jefferson KP, Gillatt DA. Hereditary urological cancer syndromes. Nat Clin Pract Urol. 2007;4(4):218–26.

5. **Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, et al. Inherited TP53 Variants and Risk of Prostate Cancer. Eur Urol. marzo de 2022;81(3):243-50.**

6. **Li FP, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res. 15 de septiembre de 1988;48(18):5358-62.**

7. **Chompret A, Abel A, Stoppa-Lyonnet D, Brugiéres L, Pagés S, Feunteun J, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet. enero de 2001;38(1):43-7.**

8. **Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 20 de julio de 2015;33(21):2345-52.**

9. **Eeles RA. Germline mutations in the TP53 gene. Cancer Surv. 1995;25:101-24.**

10. **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. 1 de marzo de 1994;54(5):1298-304.**

11. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012. Int J Cancer. 2015;136(5):E359–86.

12. Spees CK, Kelleher KJ, Abaza R, Clinton SK. Prostate cancer and Li-Fraumeni Syndrome: Implications for screening and therapy. Urol Case Rep. 2015;3(2).

13. Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2015;33(31):3660–7.

14. Yang M, Kim J-W. Principles of genetic counseling in the era of next-generation sequencing. Ann Lab Med. 2018;38(4):291–5.

15. Dowell SP, Wilson PO, Derias NW, Lane DP, Hall PA. Clinical utility of the immunocytochemical detection of p53 protein in cytological specimens. Cancer Res. 1994;54(11):2914–8.

16. Soussi T, Béroud C. Assessing TP53 status in human tumours to evaluate clinical outcome. Nat Rev Cancer. 2001;1(3):233–40.

17. The TP53 Database [Internet]. Isb-cgc.org. [Retrieved November 11 2021]. Available from: https://tp53.isb-cgc.org/

18. Zhen JT, Syed J, Nguyen KA, Leapman MS, Agarwal N, Brierley K, et al. Genetic testing for hereditary prostate cancer: Current status and limitations. Cancer. 2018;124(15):3105-17.

19. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, et al. Integrative genomic profiling of human prostate cancer. Cancer Cell. 13 de julio de 2010;18(1):11-22.

20. **Yadav S, Hart SN, Hu C, Hillman D, Lee KY, Gnanaolivu R, et al. Contribution of Inherited DNA-Repair Gene Mutations to Hormone-Sensitive and Castrate-Resistant Metastatic Prostate Cancer and Implications for Clinical Outcome. JCO Precis Oncol. 17 de septiembre de 2019;3:PO.19.00067.**

21. **Na R, Zheng SL, Han M, et al: Germline mutations in ATM and BRCA1/2 Distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 71:740-747, 2017**

22. **Castro E, Goh C, Olmos D, et al: Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 31:1748-1757, 2013**

23. **Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and Somatic Mutations in Prostate Cancer for the Clinician. J Natl Compr Canc Netw. 1 de mayo de 2019;17(5):515-21.**

24. Mottet N., Bellmunt J., Briers E., Bolla M., Bourke L., Cornford P., De Santis M., Henry A., Joniau S., Lam T., Mason M.D., Van den Poel H., Van den Kwast T.H., Rouvière O., Wiegel T.; members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines Panel. EAU – ESTRO –

ESUR – SIOG Guidelines on Prostate Cancer. 978-94-92671-13-4. Publisher: EAU Guidelines Office. Place published: Arnhem, The Netherlands, 2021.

25. Lee JM, Bernstein A. p53 mutations increase resistance to ionizing radiation. PNAS. 15th June 1993;90(12):5742-6.

26. Matsui Y, Tsuchida Y, Keng PC. Effects of p53 Mutations on Cellular Sensitivity to Ionizing Radiation. American Journal of Clinical Oncology. October 2001;24(5):486-90.

27. Kasper E, Angot E, Colasse E, Nicol L, Sabourin J-C, Adriouch S, et al. Contribution of genotoxic anticancer treatments to the development of multiple primary tumours in the context of germline TP53 mutations. Eur J Cancer. September 2018;101:254-62.

28. Churpek J, Marquez R, Neistadt B, Claussen K, Lee M, Churpek M, et al. Inherited mutations in cancer susceptibility genes are common among breast cancer survivors who develop therapy-related leukemia. Cancer. 15th January 2016;122(2):304-11.

29. Lammens CRM, Aaronson NK, Wagner A, Sijmons RH, Ausems MGEM, Vriends AHJT, et al. Genetic testing in Li-Fraumeni syndrome: uptake and psychosocial consequences. J Clin Oncol. 2010;28(18):3008–14

Figure 1 legend

Positive LFS male

Positive LFS female

Negative LFS male

Negative LFS female

Died from LFS-related cancer

LFS: Li-Fraumeni Syndrome; 1: Stomach cancer 2: Prostate cancer 3: Suprarenal cancer 4: Breast cancer 5: Uterine cancer 6: Brain cancer 7: Leukemia