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Li-Fraumeni Syndrome

Metachronous presentation of soft-tissue sarcoma, heart sarcoma and gastric cancer

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Abstract

Li-Fraumeni syndrome (LFS) is a hereditary autosomal dominant disorder with a predisposition to cancer. It is associated with abnormalities of the tumor protein p53 (TP53) gene, manifesting with a broad range of malignant neoplasms which appear at an early age. We discuss the case of a young adult in whom we did this diagnosis, and we describe the therapeutic perspectives being researched. **(Acta Med Colomb 2022; 47. DOI: https://doi.org/10.36104/amc.2022.2198).**

Key words: *Li-Fraumeni syndrome, soft-tissue sarcomas, gastric cancer, cardiac tumor.*

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Introduction

The mutated TP53 tumor suppression gene is located on chromosome 17p13 (1-3), which is now known to be present in 70% of families with LFS, as well as some families or patients with disease patterns suggestive of the syndrome. The risk of developing cancer for a patient who is a carrier of the deleterious mutation on the TP53 gene is 15% at 15 years, 80% for 50-year-old women and 40% for men of the same age (4). The significant difference between the sexes is explained by breast cancers. Genetic counseling is difficult due to the wide spectrum of cancers and their occurrence at any age, generally in young people (before the age of 45). No surveillance measures may be considered effective except those aimed at breast cancers in women over the age of 20.

Soft tissue sarcomas are uncommon, may originate in different mesenchymal tissues, account for less than 1% of all neoplasms (5), and have an even rarer primary incidence in the heart and pericardium. Approximately 50% occur in the left atrium, with the most common being undifferentiated pleomorphic sarcoma (5).

Case presentation

This was a 38-year-old male patient with no significant family history. At the beginning of 2014, a soft lesion appeared in the medial region of the left pretibial soft tissues which grew rapidly over six months to a 2.5 cm greatest diameter. Histopathology showed a "sarcomatoid fusicellular tumor," and immunohistochemistry concluded: pseudoencapsulated schwannoma with degenerative changes, S100(+), with negative extension studies. Wide local excision (WLE) was performed. Three years later he underwent a vocal cord biopsy due to dysphonia, which showed laryngeal papillomatosis and hyperkeratosis with mild dysplasia. Four years later he underwent R0 WLE of an 11 cm greatest diameter mass in the middle third of his right thigh. Immunohistochemistry confirmed an undifferentiated pleomorphic sarcoma (UPS) with 8 mitoses per 10 high power fields (HPFs), grade 2, without vascular invasion, negative for AE1/AE3, EMA, S100, SOX10, actin, and desmin; CD34, KI-67:40%. Five years later an upper GI endoscopy (UGI) was performed due to reflux, cough and progressive dyspnea, documenting a *Helicobacter pylori-negative* gastric ulcer with low-grade intraepithelial dysplasia. Concomitantly, imaging studies were conducted due to persistent dyspnea and the echocardiogram, computed axial tomography (CAT) and magnetic resonance (MR) all indicated a large solid-looking mass occupying 80% of the left atrium, measuring 43 mm at its greatest diameter. It appeared pedunculated and its base was adhered to the interatrial septum, in close contact with the anterior mitral leaflet, restricting its movement. There was preserved left ventricular systolic function, with a 60% ejection fraction, along with left ventricular inflow tract obstruction, with no outflow tract obstruction, scant pericardial effusion and scant bilateral pleural effusion. The probable diagnosis was sarcoma, with a less probable diagnosis of atypical myxoma.

Cardiovascular surgery performed an R0 WLE of the solid tumor and the left atrial appendage, corroborating adequate left ventricular function and mitral valve competence. The surgical pathology showed a tumor with a 7 cm greatest diameter in the left atrium, and the immunohistochemistry showed: high-grade (3) undifferentiated

pleomorphic sarcoma, with necrosis of 30% of the tissue, without lymphovascular invasion, 15 mitoses per 10 HPFs; and negative for AE1-3, S100, desmin, smooth muscle actin, CD34, SOX 10, myogenin, and KI-67:40%. The final diagnosis was pT4a high-grade undifferentiated sarcoma (pTNM, AJCC 8th edition). The follow up echocardiogram immediately after surgery showed: a normal-sized left ventricle, mild diffuse hypokinesia and mild septal diachronous movement, 50% EF. A month after heart surgery, a repeat UGI showed a 20 mm ulcerated lesion due to adenocarcinoma in the anterior wall of the gastric antrum; adjuvant treatment of the heart neoplasm was postponed and the patient underwent a gastrectomy with R0 excision, with a pT1b; pN; pM0 post-surgical classification, with 15 tumor-free lymph nodes resected and no need for complementary treatment. As an adjuvant for the left atrial sarcoma, he received six cycles of trabectedin infusion (an antineoplastic alkylating agent which is beneficial in sarcomas and has low cardiac toxicity) (5). Follow up studies confirmed the lack of residual lesions, with a preserved ejection fraction of 62% and a normal PET scan.

In this patient, the c.586>T; p.Ar g196* heterozygous variant was found on the TP53 gene. The patient's son was referred for genetic counseling, and the patient continued follow up according to the conventional protocol. However, his disease continued to follow its natural course; three months prior to the writing of this paper, he required a new R0 WLE in the right gluteal region.

Discussion

Cardiac sarcomas (CSs) only make up 20% of all primary cardiac tumors. The symptoms depend on the chambers and structures involved. The cardiac mass is generally found through transthoracic echocardiography. The diagnosis is made by biopsy. In the most recent histological classification, angiosarcoma is the most common malignant tumor of the heart with recognizable differentiation. Undifferentiated sarcomas represent a third of all CSs and have been incorporated into the malignant fibrous histiocytoma/pleomorphic sarcoma subgroup (6). Sarcomas, which mainly occur in the left atrium, are dependent on the endocardium and make up 50% of the CSs, with the most common being undifferentiated pleomorphic sarcoma. On a lesser scale, they occur in the left ventricle and right atrium. Using cardiac imaging, these tumors are easily distinguished from myxomas (benign tumors, dependent on the endocardium with somatic mutations of the PRKAR1A gene), as the CSs infiltrate the atrial wall and lack an insertion site on the atrial septum (6). Sarcomas are histologically heterogenous; when fusiform fibroblast-like cells on a myxoid or fibrous background predominate, they are known as myxofibrosarcomas and have a better prognosis. Less commonly, leiomyosarcomas, synovial sarcomas and extraskeletal osteosarcomas may occur in the left atrium.

Left atrial sarcomas have been associated with amplification of the MDM2 proto-oncogene, the E3 ubiquitin-protein ligase gene (MDM2), intimal sarcoma and embolic phenomena. The fundamental reason behind the use of this term for CSs is that MDM2 amplification, which had previously been restricted to liposarcomas and a small number of other sarcomas, was recently found in the majority of sarcomas of the "intima" of the pulmonary artery and in undifferentiated cardiac sarcomas. The "conventional" treatment for non-cardiac sarcomas involves complete surgical excision (stereotomy/cardiopulmonary bypass under cardioplegic arrest), followed by radiation therapy and chemotherapy (6).

Cardiac sarcomas have a poor prognosis, with a mean survival ranging from 9.6-1.5 months (7). A less aggressive course seems to be related to a location in the left atrium, low histological grading with scant cellular pleomorphism and low mitotic activity, lack of necrosis, a myxoid tumor appearance and no metastasis at the time of diagnosis. If complete surgical resection of the cardiac sarcoma is not possible (as often occurs), more than 90% of patients die within one year regardless of any post-surgical treatment. Extracardiac metastasectomies are left as palliative measures. Due to the rare number of patients, there are no specific clinical trials; the chemotherapy protocols are derived from extracardiac soft tissue sarcoma data, with the most common of these including anthracyclines, ifosfamide and taxanes. However, a large initial meta-analysis of studies of adjuvant chemotherapy in extracardiac sarcomas found no survival benefit for soft tissue sarcomas in adults (7). In this case, and even taking into account the previous considerations and weighing the risk-benefit of a new intervention, it was decided to treat the patient with the alkylating agent trabectedin. An excellent tolerance and minimal toxicity were achieved, with a preserved ejection fraction and no cardiac relapse.

A heterozygous c.586>T;p.Ar g196* variant in the *TP53 gen*e was found in this patient. This detected variant creates a premature termination codon which results in a truncated protein or degraded mRNA transcripts (by nonsense). This variant has been reported in many individuals and families affected by Li-Fraumeni-like syndrome, including patients affected by sarcoma. In the ClinVar database, the variant has consistently been classified as pathogenic (9). "Normally," the TP53 gene codes for tumor suppressor p53, which is involved in controlling the cell cycle when there is DNA damage and halts the cell cycle when it detects DNA damage. P53 may also activate DNA or gene repair, or cause apoptosis when there is DNA damage; it has been termed the "cellular guardian." The pathogenic TP53 variants cause autosomal dominant Li-Fraumeni cancer-predisposition syndrome which is associated with a spectrum of malignant neoplasms in children and adults (10).

There are currently no FDA-approved treatments aimed at p53. Since the TP53 mutations which promote cancer

have lost their repair function, a drug would be needed to increase p53 function. An approach which is being tested in cancers with low p53 expression is the use of a class of drugs known as nutlin-3 small molecules, which act by occupying the MDM2 p53 binding pocket. The nutlins bind to MDM2 and prevent p53 binding and ubiquitination (to avoid the action of the recycling protein known as "ubiquitin"), and impede its degradation, thus increasing p53 levels and in this way promoting signals to avoid inappropriate divisions and cancer cell apoptosis.

MDM2 binds to the p53 tumor suppressant protein with high affinity and negatively modulates its transcriptional activity and stability. The overexpression of MDM2, which is found in many human tumors, profoundly alters p53 function. The inhibition of MDM2-p53 interaction can stabilize p53 and may offer a new strategy for cancer treatment (12). Thus, the accumulation of p53 within the cellular nuclei through the use of nutlins has proven effective in squamous cell carcinoma cell lines of the head and neck, and has also achieved positive regulation of p21 expression which halts the cell cycle, increasing the therapeutic efficacy of chemotherapy (11).

While studies continue, for now the management of LFS-related cancers generally follows the standard treatment protocols and minimizes radiation when possible. Likewise, the association of early detection with better long-term survival in these patients is emphasized. Treatment is aimed at the type of cancer and is the same for any patient with or without the syndrome. However, due to the unique characterization of this syndrome, there are parameters which must be taken into account according to the risk-benefit of each case, such as in cases with an indication for radiation therapy, since the risk of developing another cancer increases (14). The 2020 European guidelines recommend performing a clinical exam and abdominal ultrasound every six months on children with the *TP53* variant, along with annual whole-body magnetic resonance imaging (WB-MRI) and cerebral MRI beginning in the first year of life. Adults should have an annual clinical exam, WB-MRI, breast MRI in women 2-65 years old, and brain MRI up to 50 years old (15, 16).

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