WHEN RARE GETS COMMON: LEIOMYOSARCOMAS IN THE BRAZILIAN LI-FRAUMENI SYNDROME VARIANT

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INTRODUCTION

Leiomyosarcomas (LMS) are tumors that can originate from smooth muscle cells or their precursors, and can be diagnosed in various organs and systems, accounting for 5–10% of soft tissue sarcomas (STS). These tumors are part of the cancer spectrum associated with Li-Fraumeni Syndrome (LFS), a hereditary cancer predisposition condition caused by pathogenic (PV) or likely pathogenic germline variants (LPV) in the TP53 gene. In Brazil, there is a notably high prevalence of the founder variant TP53:c.1010G>A (p.Arg337His), also known as the Brazilian variant. Among adult carriers of this variant, LMS is the most prevalent type of sarcoma.

OBJECTIVES

- To evaluate the clinical and histopathological characteristics of LMS in patients with the germline variant in the TP53 gene TP53:c.1010G>A:p.Arg337His.
- To compare the clinical presentation of LMS in the Brazilian founder variant TP53:p.Arg337His with the presentation in patients carrying other germline TP53 variants.
- To describe the occurrence of LMS in patients with LFS with multiple primary tumors recorded in BLiSS.

METHODS

It is a cross-sectional, observational, and descriptive study that evaluated individuals over 18 years old with histopathologically confirmed LMS and a molecular diagnosis of LFS, registered in the Brazilian Li-Fraumeni Syndrome Study (BLiSS) database at Hospital Sírio-Libanês. The sample is derived from BLiSS counts with 26 individuals with LFS and LMS and was obtained for the present study, from February to May 2024.

RESULTS AND DISCUSSION

Individuals with LFS show an increased predisposition to LMS, particularly carriers of the Brazilian TP53 R337H variant. LMS diagnoses occur at earlier ages than in the general population, although patients with the R337H variant tend to present later than those with non-R337H variants. The mean age for an oncologic diagnosis was 55,2, the youngest diagnosis at 27 and the oldest at 79. In this cohort, LMS emerged as the most prevalent subtype of sarcoma, predominantly high-grade and retroperitoneal in location.

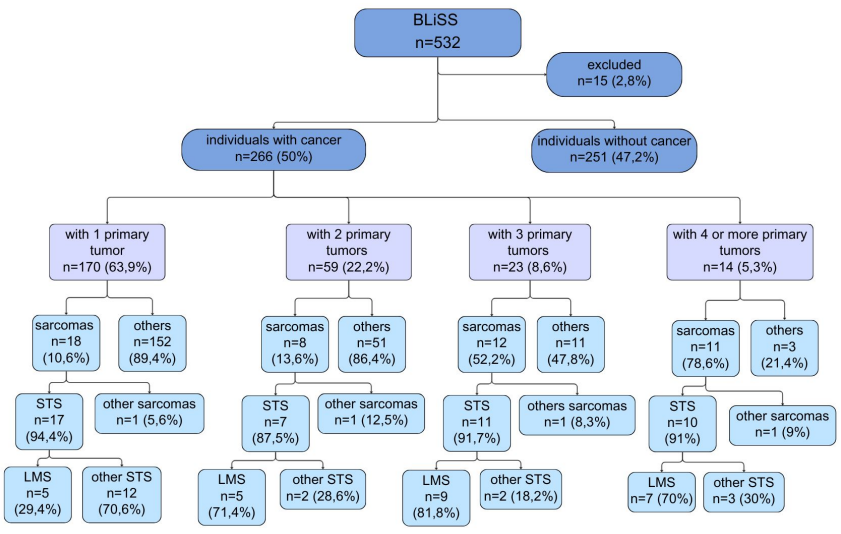
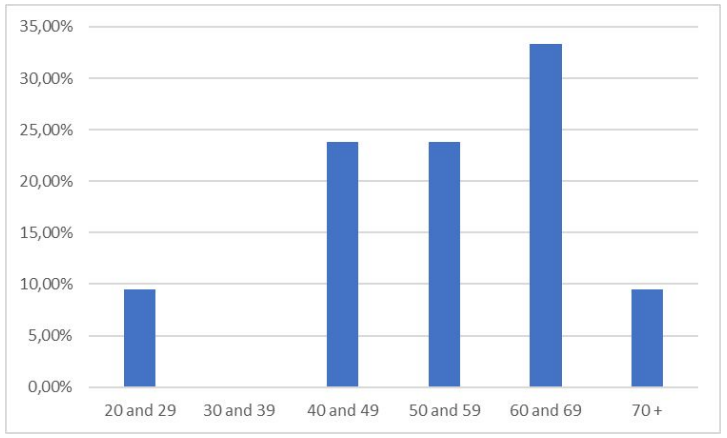
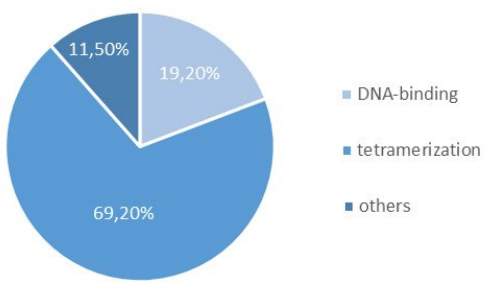


Chart 1: Age rage of diagnosis in individuals with R337H variant



The analysis of the distribution of different types of sarcomas among individuals with multiple primary tumors suggests an increasing trend in the frequency of LMS as the number of primary tumors rises. Among individuals who developed only one primary tumor, 67% had non-LMS SPM, while LMS accounted for 28% and other sarcomas for 5%. However, a shift in distribution is observed as the number of primary tumors increases.The reduced penetrance of the R337H variant may contribute to longer survival, thereby increasing the likelihood of developing multiple LMS, with carcinogenesis potentially driven by impaired p53 tetramerization.

Chart2: variants distribution in p53 domains



LMS topography in R337H sample (n=21 LMS)

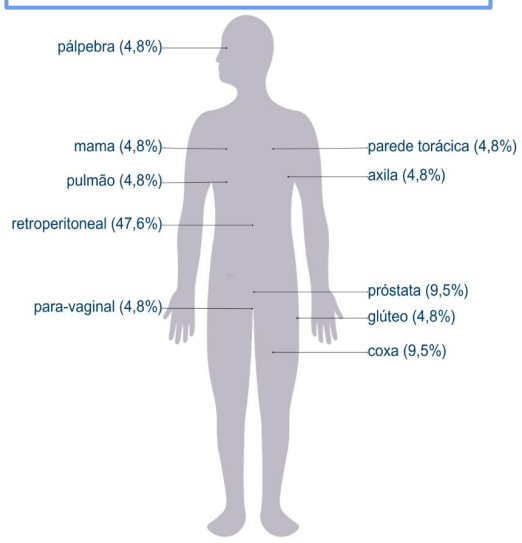


Table 1: Description of retroperitoneal LMS sites with their respective numbers and percentages of the total RP-LMS sample

Description of RP-LMS	colon	1	9,1%
	paraovarian	2	18,2%
	kidney	1	9,1%
	ureter	1	9,1%
	inferior vena cava	3	27,3%
	gonadal vein	1	9,1%
	iliac vein	2	18,2%

*for 3/14 RP-LMS the specific site information wasn't available

The analysis of the topographies of LMS revealed a predominance of retroperitoneal LMS, followed by LMS in the extremities in the total sample (n=33), and trunk LMS in the sample of individuals with the Brazilian variant R337H (n=21). The peritoneal topography as the most frequent is consistent with what is described in the literature. Complete surgical resection (R0) was effective in most cases, underscoring its importance for disease control and prognosis. Nevertheless, the study is limited by its small sample size, the absence of standardized pathology review, and the underrepresentation of pediatric patients. Overall, these findings emphasize the importance of standardized diagnostic strategies and further molecular investigations into LMS within the context of hereditary cancer predisposition.

CONCLUSION

The age of diagnosis in these individuals was 11 years later compared to carriers of other pathogenic TP53 variants, reinforcing the reduced penetrance of the Brazilian variant. However, all individuals were diagnosed with high-grade LMS at the time of diagnosis. The most frequent site was retroperitoneal, followed by trunk LMS.LMS are the most frequent SPM in the Brazilian variant of SLF. The analysis of multiple primary tumor occurrence showed an increasing trend of LMS among individuals with two or more tumors, suggesting that, in addition to a predisposition to multiple primary tumors, there may be specific molecular mechanisms favoring the occurrence of LMS in these patients. The study reinforces the importance of surveillance through screening exams as proposed by the Toronto Protocol, as well as the importance of clinical examination and multidisciplinary follow-up for individuals with the Brazilian variant of SLF, with attention to the risk of developing LMS throughout life.

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