

Case report

Ischemic stroke from non-bacterial thrombotic endocarditis embolization in Li-Fraumeni syndrome: A case report

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Abstract

Objective: Li-Fraumeni Syndrome (LFS) is a rare autosomal-dominant syndrome caused by a heterozygous germline mutation of the TP53 gene. It is characterized by early-onset malignancies and high penetrance. Non-bacterial thrombotic endocarditis (NBTE) is an uncommon condition for which cancer is a significant risk factor.

Here we present a complex case of LFS unveiled by a NBTE-related ischemic stroke.

Case presentation: A 41-year-old woman was admitted following a syncopal episode, preceded by a history of ischemic stroke. She had a notable family history of cancers. Imaging studies revealed ischemic damage and hemorrhagic infarcts, indicating a possible embolic origin or neoplastic involvement. Subsequent examinations revealed a NBTE on the aortic valve as well as multiple primary malignancies including high-grade invasive ductal carcinoma in the breast and primary lung adenocarcinoma. Genetic testing confirmed the presence of a pathogenic variant in TP53.

Conclusion: This case underscores the intricate interplay between LFS, oncological manifestations, and thrombotic complications leading to ischemic stroke through NBTE embolization.

Key words: Li-Fraumeni syndrome, non-bacterial thrombotic endocarditis, ischemic stroke, TP53 mutation, embolization (Heart Vessels Transplant 2024; 8: doi: 10.24969/hvt.2024.487)

Introduction

Li-Fraumeni syndrome (LFS) is a rare autosomal-dominant syndrome caused by a heterozygous germline mutation of the TP53 gene. It is characterized by early-onset tumors, including bone and soft-tissue sarcomas, breast cancer, adrenocortical carcinomas, neoplasms of the central nervous system, among many others, and high penetrance (1). The prognosis of LFS is highly dependent on early detection through family history and genetic testing, as well as on prompt monitoring.

According to Villani et al. (2), 5-year survival rate was 88.8% in patients who underwent surveillance and 59.6% in the non-surveillance group. Non-bacterial thrombotic endocarditis (NBTE), formerly known as marantic or terminal endocarditis, is a serious condition for which cancer represents a substantial risk factor. It is recommended that cancer should be ruled out as a probable cause in situations when the etiology of NBTE is unknown (3, 4).

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We present a case of NBTE-related embolic stroke unveiling multifocal LFS in a 41-year-old woman.

Case presentation

In August 2022, a 41-year-old woman was admitted to our University Hospital for a syncopal episode. Written informed consent was obtained for all procedures and publication of this case report.

She had been hospitalized one month prior for ischemic stroke presenting as left facio-brachio-crural hemiparesis. She had no additional relevant medical conditions in her history, except for arterial hypertension. The patient had a family history of cancer and p53 protein mutation. One sibling was diagnosed with breast cancer at 58 years old, another sibling passed away from adrenal cancer at 46 years old, a niece was born with congenital adrenal carcinoma, while a brother who was a mutation carrier appeared to

be in good health. However, she had never been screened prior to admission.

Upon physical examination, she revealed an extensive hard nodularity in the superior-outer quadrant of the right breast. Furthermore, she displayed deep venous thromboses in both typical (right obstructive thrombosis of the soleal veins, and pre-obstructive thrombosis of the common and left superficial femoral arteries) and atypical (common hepatic artery and splenic artery thrombosis) sites.

A brain computer tomography (CT) scan revealed subacute ischemic distress with a probable embolic etiology in the territories of the right middle cerebral artery; additionally, it revealed three areas suggestive of hemorrhagic infarction in the left parietal and occipital lobes, due either to hemorrhagic angiopathy or a neoplasm of unknown localization (Fig. 1). These findings were later confirmed by brain magnetic resonance imaging (MRI) (Fig. 2).



Figure 1. Computer tomography scan revealed multiple areas consistent with ischemic tissue distress in the subacute phase, along with associated areas of hyperdensity indicative of hemorrhagic infarction

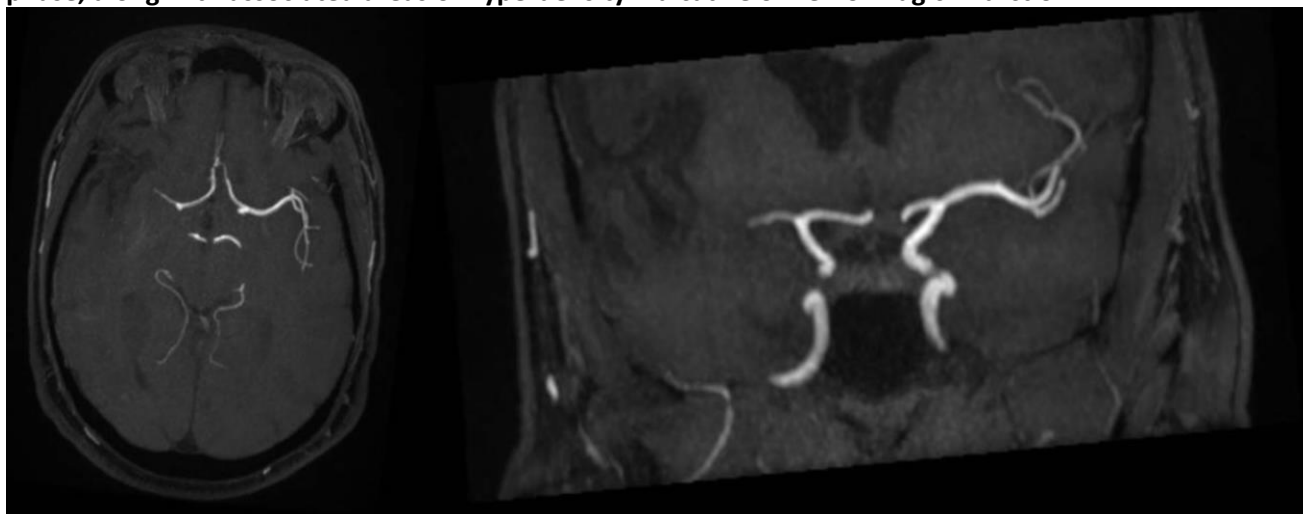


Figure 2. The magnetic resonance imaging scan revealed signs of ischemic distress of embolic origin, with extensive involvement and initial malacic transition into the territory of the right middle cerebral artery and late subacute hemorrhagic conversion of left occipito-parietal cortico-subcortical foci

Transthoracic and then transesophageal echocardiography revealed a dysmorphic aortic valve with multiple vegetating masses adhered to all aortic

valve cusps resulting in a large central coaptation deficit and subsequent severe valvular insufficiency with initial unfavorable left ventricular remodeling (Fig. 3).

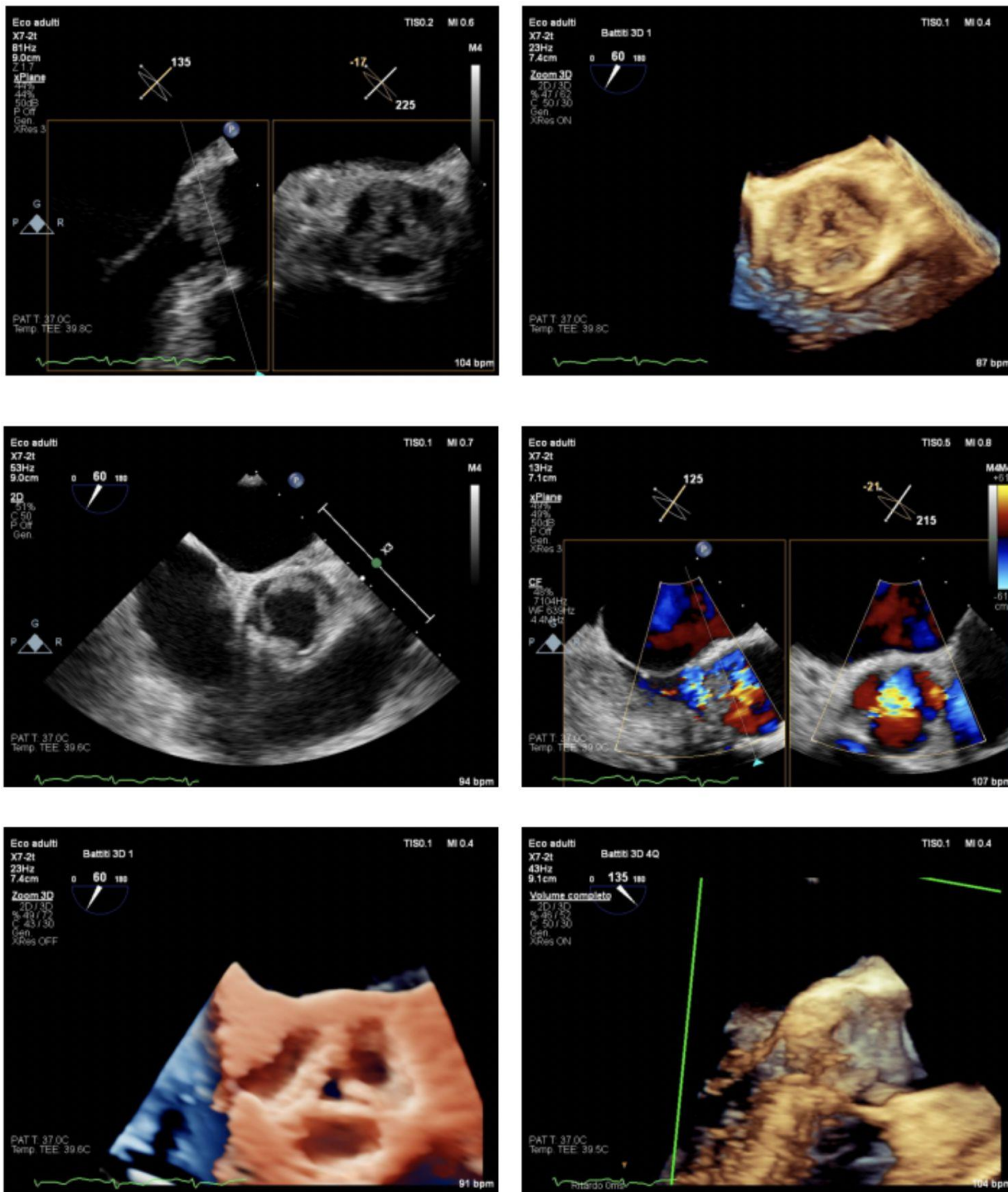


Figure 3. Transesophageal echocardiography showed alterations of the aortic valve with evidence of multiple vegetations adhered to all aortic valve cusps, predominantly at the non-coronary cusp, resulting in a large central coaptation deficit and consequent severe valvular insufficiency with initial unfavorable left ventricular remodeling

Blood culture tests were conducted to rule out infective endocarditis, and empiric antibiotic treatment was initiated. Blood cultures for bacteria including HACEK group (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*, *Coxiella*, *Bartonella*, and *Chlamidia spp.*), serologies for *mycoplasma*, *legionella*, HIV, HBV, HCV, as well as the Widal-Wright reaction tested all negative. The vegetations did not change in size with antibiotic therapy, raising the possibility of a NBTE.

In the presence of a high clinical suspicion of an underlying tumor, a total-body CT scan was performed, revealing abnormalities consistent with multiple neoplasms, which were subsequently investigated further with targeted diagnostic testing. First, several nodules with irregular margins and associated lymphadenopathy in the superior-outer and superior-inner quadrants of the right breast were found. Histologic examination of the primary lesion revealed high-grade invasive ductal carcinoma (G3) with lobular-

like growth features (E-cadherin: 20%), positive estrogen receptor (ER+: 90%), negative progesterin receptor (PR: <1%), HER2 positivity, and high proliferation index (Ki-67: 35%). Second, the right lower lung lobe displayed a solid heteroformation with irregular margins and tightly adhered to the pleura (Fig. 4A). Additional nodules and micronodules were found bilaterally. CT-guided biopsy of the major lesion confirmed the presence of a primary lung adenocarcinoma (TT1 and napsin positive, ER- and GATA3-negative). Third, a suspicious nodule was found in the right lobe of the thyroid gland (Fig. 4B), which was confirmed by ultrasonography. This finding was no further investigated. Fourth, several bone metastases were found in pelvic bones, iliac wing, femoral petrochanter region bilaterally, all sacral metameres, left clavicle, right scapula (Fig. 4C). Fifth, an additional finding was reported in the left adnexal site, however the lesion appeared with features of likely benignity.



Figure 4. Total-body computerized tomography scan showed A) a pulmonary lesion in the posterior basal segment of the right lower lobe, with the maximum axial dimensions of 40 x 30 mm and craniocaudal extension of 47 mm, B) a nodule in the right thyroid lobe (15 x 10 mm), and C) several osteolytic lesions in pelvic bones, iliac wing, femoral petrochanter region bilaterally, all sacral metameres

Upon informed consent the genetic analysis revealed the presence of the c.1010 G>A (p.Arg337His) pathogenic variant previously identified in her brother. This variant, reported in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/variation/12379/>), has been identified in several Brazilian individuals and families affected by Li-Fraumeni syndrome. Families carrying this variant show an extremely variable cancer

risk and several unaffected adult carriers have been described, suggesting an incomplete/age-dependent penetrance (5).

The case underwent collegial discussion. Any surgical interventions for the NBTE, as well as radiation therapy on the involved bone segments or stereotactic therapy on the lung lesion were excluded. The patient was therefore referred for palliative care.

Discussion

In the present case, we address a highly intricate clinical scenario of LFS presenting with NBTE-related ischemic stroke.

Individuals with LFS are lifelong susceptible to developing cancers. Overall lifetime risk is estimated to be over 70% for men and over 90% for women, and cumulative incidence is of 100% by the age of 70 (6, 7). The average age at the diagnosis of first cancers in LFS is 21.9 years, with a tendency for earlier onset in women (8). In particular, breast cancer is by far the most common cancer in women with TP53 mutation accounting for 27-31% of all LFS-related tumors (9). To date, several treatment options to reduce the incidence of cancer in LFS are under investigation on preclinical models (10), however none of them is currently available in humans (11). Therefore, individuals diagnosed with TP53 mutation necessitate a comprehensive and proactive monitoring plan to closely monitor for malignancies in different organ systems, to establish early intervention and improve the rates of survival, complications and quality of life (11). In the present case, as a result of inadequate cancer surveillance LFS manifested itself when several tumors in advanced stages had already developed.

NBTE is one of the consequences of hypercoagulable states induced by advanced malignancy (3). In NBTE, degenerating platelets interwoven with strands of fibrin lead to the formation of sterile vegetation on previously undamaged heart valves (most often aortic and mitral), without bloodstream bacterial infection (3). The most frequently malignancies associated with NBTE include mucin-secreting adenocarcinomas of the lung, stomach, biliary system, pancreas, and ovary, however association with thyroid cancer, head and neck squamous cell carcinoma has been reported in literature (3, 12). The diagnosis of NBTE is considerably more elusive than that of infective endocarditis, as there are no bloodstream markers and vegetations are smaller, easily friable and frequently embolize, leaving only small remnants to be identified through echocardiography. Embolic stroke is the most common manifestation of NBTE (3). Lopez et al. (4) addressed that 5-10 % of the patients with cryptogenic stroke have an underlying malignancy (4). The management of NBTE includes full-dose intravenous unfractionated heparin or subcutaneous low molecular weight heparin, as well as the management of underlying conditions (3). Surgery is rarely indicated since patients with NBTE

often present with advanced malignancies and therefore an unfavorable benefit-to-risk ratio (3).

Conclusion

This case highlights the complex relationship between LFS, cancer-related manifestations, and thrombotic complications. It underscores the need for a vigilant, comprehensive approach to care, emphasizing the importance of genetic counseling, personalized surveillance, and an integrated, multidisciplinary management strategy integrating oncology, genetics, cardiology, neurology, and internal medicine. As our knowledge of the genetic basis of cancer progresses, we need to adjust our strategy for handling complex hereditary cancer syndromes such as LFS.

Ethics: Written informed consent was obtained from patient for all procedures and for the publication of this case report.

Peer-review: External and internal

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Authorship: Conceptualization: SA. Investigation: SA, CM, ELC, MAN and FB. Methodology: MAN and FB. Validation: AF and AG. Visualization: SA and SC. Writing – original draft: SA. Writing – review & editing: SC and FB. Supervision: AF and AG. All authors fulfilled authorship criteria.

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