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Case Report of an Unusual Tumor in an Adult With a TP53 Germline Mutation

Julie Castiaux,[1] Isabelle Vandernoot,[2] Julie Dallemagne,[1] Marie Bruneau,[2] Mélanie Delaunoy,[2] Xavier Peyrassol,[2] Pierre Heimann,[2] Virginie De Wilde,[1] Alice Wolfromm[1]

Clinical Practice Points

- We report a unique presentation of Li-Fraumeni syndrome: the occurrence of multiple myeloma and thyroid carcinoma in a young women with a germinal TP53 truncating mutation and a non-classical personal and family history. However, there were clues in the somatic testing suggesting a germinal origin: high mutational load of TP53 (over 50%), same TP53 mutation in 2 different cancers and TP53 mutation identified as one of 14 "hotspot" TP53 germinal mutations. We insist on the refractory nature of this Li-Fraumeni syndrome-associated multiple myeloma.
- Despite the introduction of new treatments, such as daratumumab and carfilzomib, which showed improved overall response rates even in patients with high-cytogenetic risk, and venetoclax, which demonstrated an overall response rate of 40% in multi-treated myelomas, particularly t(11;14), the patient still had very poor outcome.
- Although new agents have revolutionized the management of multiple myeloma, we show that this particular case did not respond well, with the same overall survival as biallelic mutated sporadic myeloma.

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Introduction

Li-Fraumeni syndrome (LFS) is a genetic disorder that increases the lifetime risk of developing a wide spectrum of tumors, owing to a germline mutation of the TP53 tumor suppressor gene. Several studies have described the spectrum of tumors associated with LFS, mainly breast carcinoma, soft tissue sarcoma, osteosarcoma, central nervous system tumors, and adrenocortical carcinoma. With regard to hematologic disease, LFS is mainly associated with leukemia and lymphoma. In contrast, multiple myeloma (MM) is rarely known to be associated with a constitutional genetic susceptibility.

Case Report

We report the case of a 36-year-old woman diagnosed almost simultaneously with MM and thyroid cancer, both tumors carrying the same mutation in the TP53 gene (c.916C>T; p.Arg306*). LFS was suspected, and the presence of the mutation in leukocyte DNA supported this hypothesis. The germinal status of the mutation was then proven with its detection in DNA extracted from healthy fibroblasts. This case of adult-onset LFS demonstrates an unusual tumor spectrum, presenting with 2 cancers that are not commonly described in this syndrome.

The patient's family history included the fact that her mother was diagnosed with brain cancer at the age of 28, but no further information. The patient did not have any further medical history.

Thyroid Carcinoma

The patient suspected a thyroid nodule by auto-palpation. An assessment by ultrasound and puncture confirmed the presence of a nodule with grade 2 follicular proliferation. A computed tomography/positron emission tomography scan demonstrated metabolic evidence for a voluminous malignant lesion in the right thyroid lobe, with diffuse axial and appendicular osteomedullary involvement. Thyroidectomy and right lymph node dissection were performed. The anatomopathology report concluded that the tumor was a follicular carcinoma of the thyroid gland with an oncocytic variant. A TP53 mutation was identified by next-generation

[1]Department of Hematology
[2]Department of Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

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Address for correspondence: Julie Castiaux, MD, Department of Hematology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
E-mail contact: julie.castiaux@ulb.be

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sequencing of the tumoral tissue. The mutational load (allelic frequency) was 86% in DNA extracted from the thyroid surgical specimen and 57% in DNA extracted from adjacent healthy thyroid tissue, suggesting a germinal mutation with loss of the second allele in the tumor.

Multiple Myeloma

The clinical presentation of the patient's MM was not unusual. She had costal and spinal pain that evolved for several weeks, and recent paresthesia of the lower limbs with electric shock sensation at the lumbar level. Laboratory testing demonstrated hypercalcemia at 2.94 mmol/L with acute renal failure (creatinine, 1.4 mg/dL; CDK-EPI, 46 mL/min/1.73m^2). Urinalysis showed proteinuria with 7.4g/g creatinine, 99% globulin with Bence Jones positivity. Thoracic computed tomography revealed multiple osteolytic lesions in the body of the thoracic and lumbar vertebrae. Protein electrophoresis revealed hypogammaglobulinemia. An increase in lambda chains at 665.14 mg/dL and a decrease in kappa/lambda ratio of 0.000767 was observed. Twenty-six percent monoclonal lambda plasma cells were found at bone marrow aspiration. Massive parallel sequencing of a gene panel detected the c.916C>T (p.Arg306*) mutation of the TP53 gene, the same mutation that was found in the thyroid carcinoma. Cytogenetics by fluorescence in situ hybridization identified a 1q duplication and a deletion of the TP53 gene. The medullary karyotype was found to be a complex karyotype with monosomy 17 associated with t(11;14) translocation.

The patient received 5 treatment lines,[1,2] including new agents such as daratumumab, carfilzomib, and venetoclax and high-dose chemotherapy D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide), but relapsed each time (see Figure 1). An autologous stem cell transplantation was performed after D-PACE (which was the most effective treatment), but that did not prevent disease progression. She died 1 year after diagnosis.

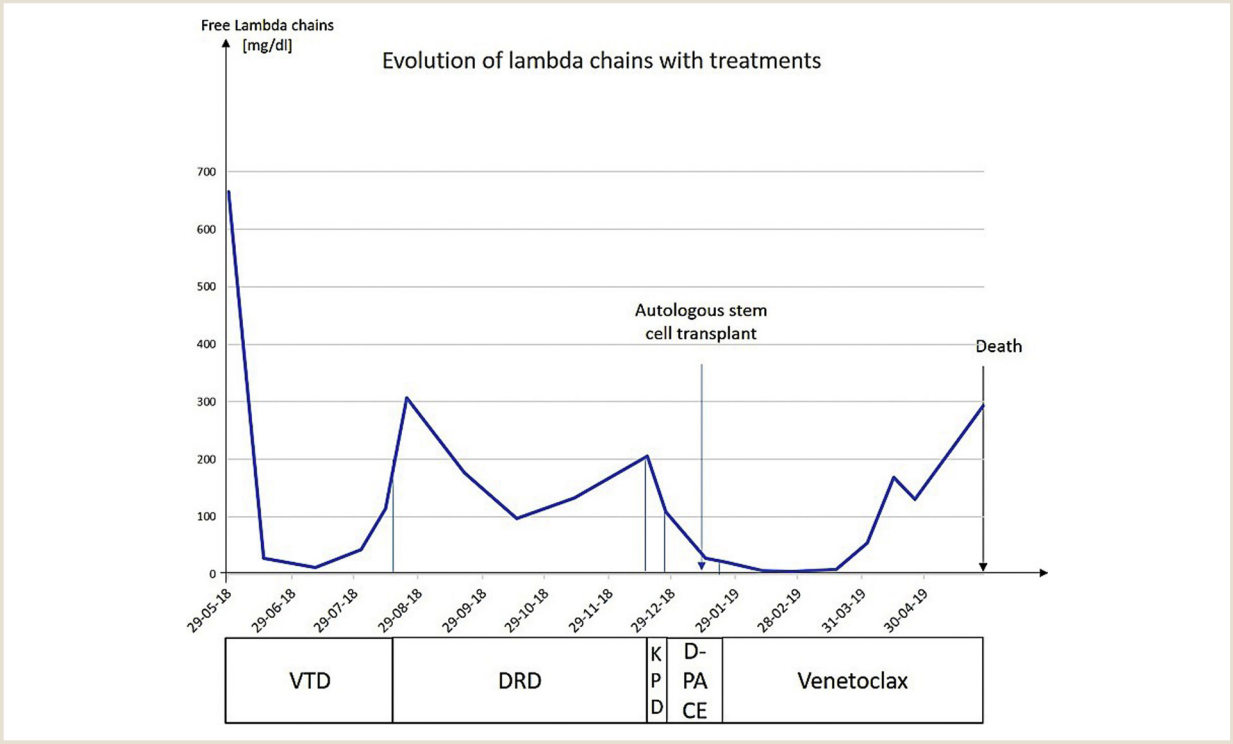
The refractory nature of this LFS-associated MM is remarkable. Despite the introduction of new treatments, such as daratumumab and carfilzomib, which showed improved overall response rates even in patients with high-cytogenetic risk,[3,4] and venetoclax, which demonstrated an overall response rate of 40% in multi-treated myelomas, particularly t(11;14),[5] the patient still had very poor outcome. Thus, overall survival was not improved with these new agents.[3-5]

Discussion

The association of LFS with MM is unexpected given its low proliferation index compared with leukemias.

To our knowledge, only 1 case of MM has been described previously in the literature among patients with LFS (ie, only one 43-year-old patient, among 219 cases, developed MM).[6] Thus, it is quite unusual to present with MM in the context of LFS, which is more often associated with leukemia and lymphoma with regard to hematologic diseases.[7] In general, leukemias in patients with LFS are classically reported in young adults.[7]

Figure 1 Evolution of Lambda Chains With Treatment



Abbreviations: D-PACE = dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide; DRD = daratumumab, revlimid, and dexamethasone; KPD = carfilzomib, pomalidomide, and dexamethasone; VTD = velcade, thalidomide, and dexamethasone.

Thyroid carcinoma is not one of the original classic LFS cancers.[8] However, this cancer has been routinely reported in LFS families.[6,9] A Brazilian study in 2017 reported a prevalence of 10.9% thyroid carcinoma among patients with LFS with the p.R337H mutation.[8] A more recent study that has not selected patients on the basis of classic criteria also reports thyroid carcinoma as an LFS-associated cancer.[10]

Somatic TP53 Mutations in MM

TP53 is a tumor-suppressor gene.[11] Although mutations in TP53 are inherited in an autosomal dominant manner in families with LFS, its oncogenic functions at the somatic level are exerted according to a biallelic model, following the Knudson hypothesis.[12] The 2-hit model is the hypothesis that a cell requires bi-allelic mutations to cause a phenotype; in this case, DNA damage leading to tumor development. A second hit was indeed observed in the bone marrow cells, harboring a TP53 deletion (monosomy of the entire chromosome 17), leading to loss of heterozygosity (LOH) of the c.916C>T mutation.

In sporadic cases of MM, the presence of TP53 somatic mutations in newly diagnosed MM is frequent (10% 17p13 deletion; 3% other mutations) even though a mono-allelic TP53 event is a controversial risk factor, in contrast to bi-allelic hits.[13] A mono-allelic 17p13 deletion could lead to haploinsufficiency of the p53 protein; yet all 17p13 deletions are not equal, the effect depending mainly on the remaining expression level of the protein. Other mechanisms, such as hypermethylation of the wild-type gene's promoter could account for the LOH.[14]

In any case, the combination of 2 hits is associated with poorer survival (19 vs. 74 months, in del(17p) patients, with and without TP53 mutations, respectively). The appearance of a TP53 mutation in a patient who already has a deletion is often associated with a relapse and poor prognosis.[15] It is likely that survival in patients with LFS is poor because of their likely "double-hit." in parallel with TP53 double-mutated patients at the somatic level (without LFS).

TP53 Mutation Classification and LFS

There are different types of mutations: missense mutations, nonsense mutations, splicing mutations, frameshift deletions/insertions, in frame deletions/insertions, and genomic rearrangements. For certain diseases, missense mutations can cause a dominant-negative effect, (ie, alteration of the second wild-type allele). In LFS, missense mutations have, in general, a more aggressive phenotype, resulting in cancers affecting younger people (children and young adults), a higher penetrance, and more severe expression.[6,11]

The mutation found in our patient was a nonsense mutation (base substitution leading to appearance of a stop codon and a truncated protein), resulting in a loss-of-function effect. A review described the mutation identified in this case as one of 14 "hotspot" TP53 germinal mutations, with a reported penetrance of 50% at 30 years and 75% at 50 years.[11]

This case does not meet current criteria for TP53 testing: the classical criteria of LFS[11] are not fulfilled, nor are Chrompret's criteria or Li-Fraumeni-like syndrome criteria.[6,16] These different criteria are mainly based on the presence of cancers belonging to the LFS tumor spectrum, multiple cancers, age at cancer diagnosis, and family history of cancer. Regarding familial history, we suspect maternal inheritance of the mutation because the cerebral neoplasia of the mother is a cancer known to be associated with the syndrome. We also note that the patient was only 36 years old at diagnosis, which is very young, taking into account that the proportion of patients under 40 years with MM is less than 2%, and the median age at the diagnosis is around 66 years.[17] However, there were clues in the somatic testing suggesting a germinal origin. First, high mutational load of genes predisposing to hereditary cancer (over 50%) suggests germline mutations.[18] In this case, the mutational load was 86% in the thyroid cancer. Secondly, we found the same TP53 mutation in 2 different cancers. Finally, the TP53 mutation was identified as 1 of 14 "hotspot" TP53 germinal mutations. These different elements should probably be considered in clinical practice.

Conclusion

We report a unique presentation of LFS: the occurrence of MM and thyroid carcinoma in a young woman with a germinal TP53 truncating mutation and a non-classical personal and family history. However, there were clues in the somatic testing suggesting a germinal origin.

Although new agents have revolutionized the management of MM, we show that this particular case did not respond well, with the same overall survival as biallelic mutated sporadic myeloma.

Disclosure

The authors have stated that they have no conflicts of interest.

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