

Cirrhosis caused by RTEL1-Associated Telomeropathy

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Abstract

Telomere biology disorders (TBDs), or telomeropathies, are rare genetic conditions caused by defective telomere maintenance, leading to accelerated telomere shortening, premature cellular senescence, and multi-organ dysfunction(1,3). The clinical spectrum ranges from dyskeratosis congenita to pulmonary fibrosis, bone marrow failure (pancytopenia, leukemia, myelodysplasia), and cirrhosis(2,4). Overall, up to 40% of TBD patients present various hepatic manifestations such as cirrhosis (7%), nodular regenerative hyperplasia and steatohepatitis (5). (*Acta gastroenterol belg.*, 2026, 89, 493-494).

Keywords: Telomere biology disorders, RTEL1, cirrhosis, Flow-FISH.

Introduction

TBDs result from mutations in telomere-related genes (RTEL1, TERT, TERC...) with autosomal dominant or recessive inheritance. Most are heterozygous; homozygous mutations, such as in Hoyeraal-Hreidarsson syndrome, cause earlier and more severe disease. RTEL1 encodes a DNA helicase essential for telomere maintenance and genomic stability (1, 4).

We report here a novel heterozygous RTEL mutation causing cirrhosis with multi-systemic features.

Case presentation

A 64-year-old woman was referred at our outpatient clinic with compensated cirrhosis (Child-Pugh A5), incidentally discovered during cholecystectomy. Liver biopsy confirmed cirrhosis with moderate steatosis, mild hepatocellular ballooning, and nonspecific granulomatous inflammation identified by CD68 immunohistochemistry (location not specified).

Her medical history included thyroid cancer, high blood pressure, dyslipidemia, without alcohol or hepatotoxic drug exposure. Family history revealed cirrhosis in three brothers. One died after requiring liver transplantation for hepatocellular carcinoma. He also had pulmonary fibrosis and his daughter died at 42 from cirrhosis. A second brother died of leukemia. The third one has well-compensated cirrhosis.

Clinical examination was normal. Laboratory tests showed isolated pancytopenia (hemoglobin 10.4g/dL, platelets 81.000/ μ L, neutrophils 1341/ μ L). Liver function tests were normal.

Given the family history, telomeropathy-associated cirrhosis was suspected. Telomere length measurement by Flow-FISH revealed short telomeres (1st–10th percentile). Genetic testing identified a novel heterozygous pathogenic RTEL1 variant (c.2471_2476delinsTCATA;p.Pro824Leufs*80), confirming autosomal dominant telomeropathy-associated cirrhosis.

Follow-up showed stable liver function and persistent pancytopenia. HCC screening was consistently negative. Imaging revealed thoraco-abdominal lymphadenopathy without metabolic activity. Lymph node fine-needle aspiration revealed granulomatous lymphadenopathy, with no evidence of malignancy; etiology remains unknown despite extensive workup.

Discussion

This case illustrates the importance of considering telomeropathy in cryptogenic cirrhosis when associated with compatible features such as suggestive family history. Our patient presented several features of RTEL1-telomeropathy: pancytopenia, cirrhosis, and a strong familial clustering of liver, pulmonary and hematologic disease (4, 5).

Flow-FISH remains the gold standard for telomere length assessment, with short telomeres defined below the 10th percentile (1). In Belgium, its reimbursement since 2023 in cryptogenic cirrhosis represents a major step toward earlier recognition of telomeropathies.

Genetic testing identified a novel heterozygous RTEL1 frameshift variant, expanding the known mutational spectrum. RTEL1 loss-of-function impairs telomere maintenance, leading to premature cellular senescence and fibrosis (2, 4). While many RTEL1 mutations are documented, this variant appears unreported and is not listed in ClinVar.

The patient presented granulomatous lymphadenopathies and hepatic granulomas, atypical characteristics for telomeropathies. In the absence of

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other causes and given the systemic immune involvement in TBDs, an immune-mediated link is possible. TBDs may involve immune dysfunction, but evidence remains limited and further research is needed (4).

Therapeutic options remain limited outside transplantation. Androgens (Danazol) may slow telomere shortening, but hepatic efficacy is unclear, and side effects can be significant (6). Multidisciplinary care of patients with telomeropathy is essential.

Conclusion

RTEL1-associated telomeropathy remains an underestimated cause of cryptogenic cirrhosis. In this case, the combination of pancytopenia and striking family history raised suspicion and led to targeted investigations. This highlights the importance of detailed clinical evaluation, including family and extrahepatic history. In Belgium, the recent reimbursement of telomere testing for unexplained cirrhosis permits earlier diagnosis.

Greater awareness and further research are essential to improve recognition and treatment of TBDs.

Declarations

The authors have no conflicts of interest to declare.

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