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Large Cell Change in a Small Liver: A Histological Clue to Short Telomere Syndromes?

Steven M. Johnson ,[1] Katrina A. McGinty,[2] Paul H. Hayashi,[3] and Eizaburo Sasatomi[1]

Telomeres are DNA-protein complexes at the ends of chromosomes essential for maintaining genetic stability. Defects in genes coding telomere maintenance proteins rarely occur, resulting in accelerated telomere shortening. Termed short telomere syndromes (STSs), these conditions have diverse clinical manifestations, including premature hair graying, bone marrow failure, pulmonary fibrosis, early-onset malignancy, and cirrhosis. However, liver histopathological changes have not been thoroughly described in STS patients. Here, we report on a case of a patient with clinically suspected cirrhosis and striking hepatocyte large cell change (LCC) on liver biopsy who was found to have an underlying STS.

Case Report

A 39-year-old white man was referred for a diagnosis of aplastic anemia. His mother had anemia and cirrhosis and died of colon cancer at age 43, and his sister had an unclear blood dyscrasia and died at age 40. The patient had gray hair, but an otherwise unremarkable physical examination.

Abdominal computed tomography (CT; Fig. 1A,B) identified ascites, splenomegaly, and a small, nodular liver suspicious for cirrhosis. His liver volume (Fig. 1C) was 1,148 cm^3, which was 51% of expected (2,229 cm^3) based on height (1.88 m) and weight (109.3 kg). Hemodynamic analysis showed a hepatic venous pressure gradient of 13 mm Hg, consistent with portal hypertension. He had normal liver function tests and negative hepatitis serologies. Liver biopsy revealed LCC of 40%-50% of hepatocytes (Fig. 2A,B). Ten percent of hepatocytes were binucleated, and occasional cells contained more than two nuclei (Fig. 2C). Only minimal-to-focal mild portal mononuclear inflammation was observed. Trichrome staining (Fig. 2D) revealed mild portal and periportal fibrosis without nodularity or cirrhosis.

At this point, an STS was considered as a possible etiology to explain the collective findings. Tandem flow/fluorescence *in situ* hybridization (FISH) analysis revealed telomere lengths below the first percentile for age (Fig. 2E). Germline sequencing discovered a heterozygous missense variant of uncertain significance (VUS) in the telomerase reverse transcriptase (*TERT*) gene (c.301T>G, p.Phe101Val). At last follow-up 2 years later, the patient was continuing cyclosporine and eltrombopag and was transfusion dependent.

Discussion

Hepatocyte LCC is an age- and senescence-related phenomenon caused by cellular replicative exhaustion.[1,2] For instance, hepatocyte nuclear size increases

Abbreviations: CT, computed tomography; FISH, fluorescence in situ *hybridization; LCC, large cell change; STSs, short telomere syndromes.*

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Consent: No consent was sought in this report, given that the patient was anonymized and is not identifiable from the details presented in this article.

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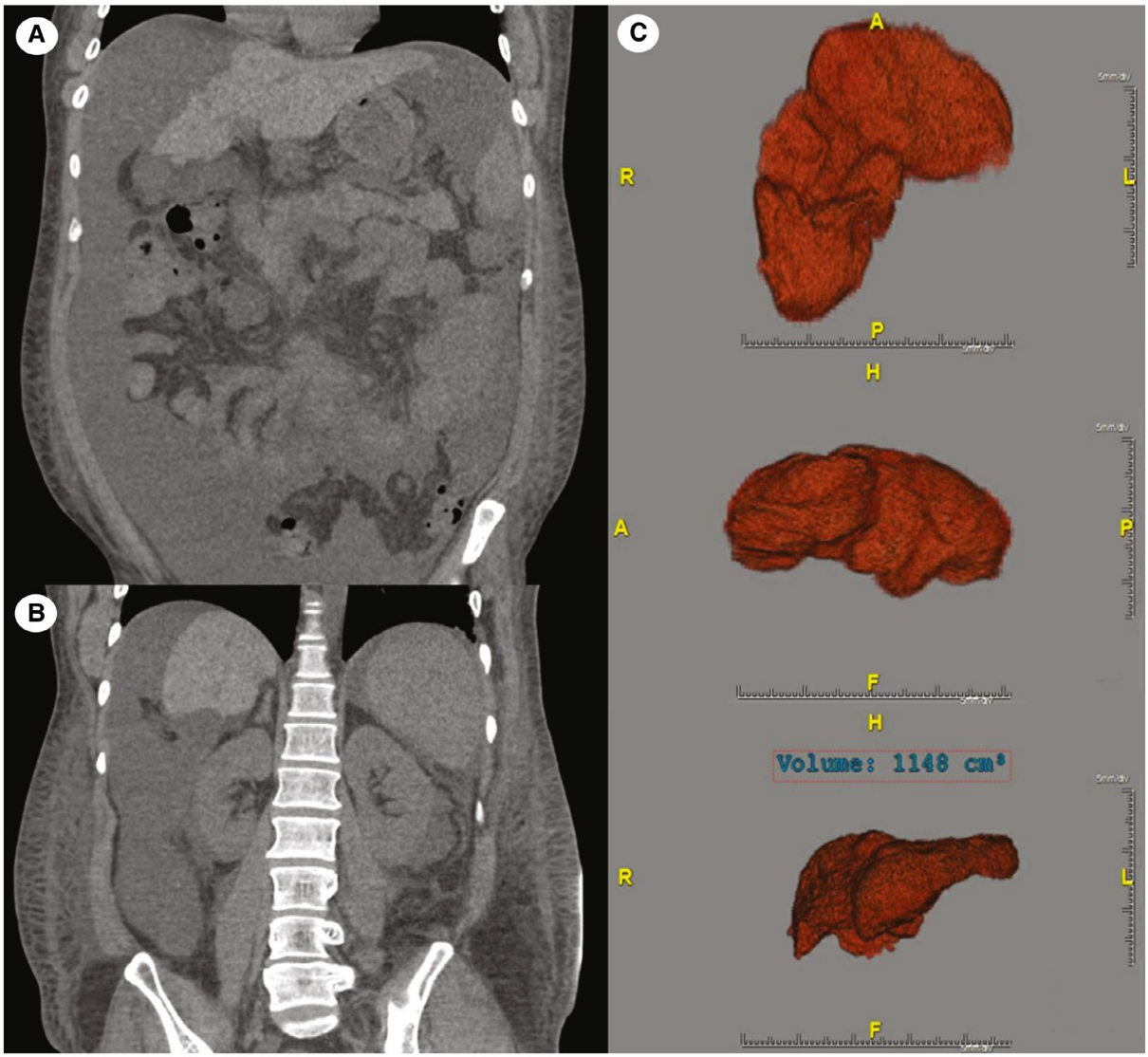

FIG. 1. Abdominal CT images, with coronal views showing (A) a small, nodular liver with ascites and (B) splenomegaly. (C) Rendering of combined CT images of the liver in the axial (top), sagittal/oblique (middle), and coronal (bottom) planes. By manual image analysis, the patient's liver volume was calculated to be 1,148 cm^3 (expected 2,229 cm^3 based on height and weight).

ARTICLE INFORMATION:

From the [1]Department of Pathology and Laboratory Medicine, The University of North Carolina School of Medicine, Chapel Hill, NC; [2]Department of Radiology, The University of North Carolina School of Medicine, Chapel Hill, NC; [3]Department of Medicine, Division of Gastroenterology and Hepatology, The University of North Carolina School of Medicine, Chapel Hill, NC.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Eizaburo Sasatomi, M.D., Ph.D.
Department of Pathology and Laboratory Medicine
University of North Carolina at Chapel Hill
303 Brinkhous-Bullitt Building, CB#7525
Chapel Hill, NC 27599
E-mail: eizaburo_sasatomi@med.unc.edu
Tel.: +1-984-974-7176

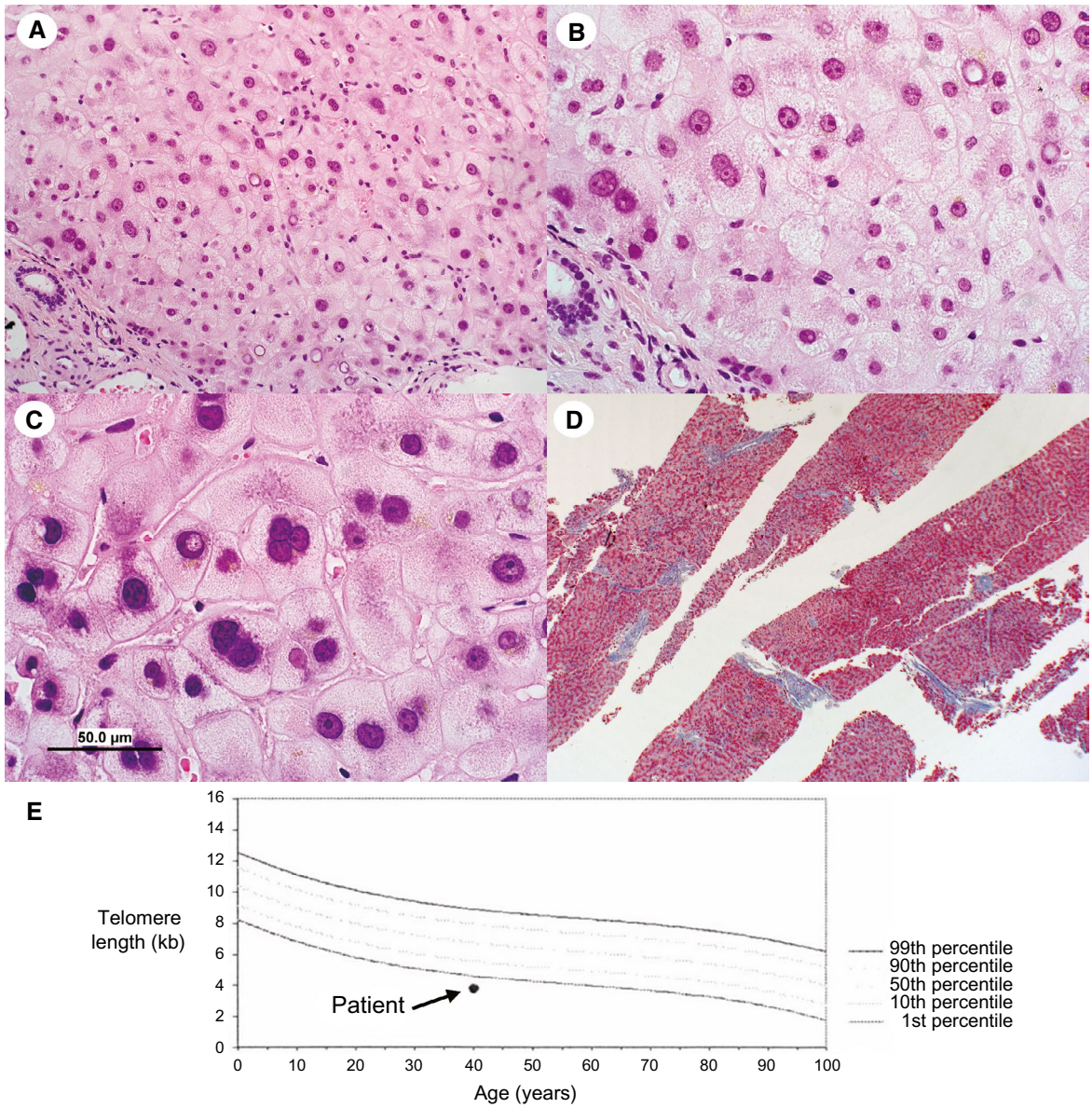

FIG. 2. (A) The liver biopsy at low magnification showed marked anisonucleosis and anisocytosis attributed to the presence of many large hepatocytes, without significant portal or lobular inflammation. (B) Enlarged hepatocytes (top left) displayed large nuclei with a preserved nuclear-to-cytoplasmic ratio compared to relatively normal-sized hepatocytes (bottom right). (C) Many of the enlarged hepatocytes were >2-4 times larger than normal, and at least 10% of hepatocytes were bi- or multinucleated. (D) Trichrome stain highlights mild portal and periportal fibrosis, but shows no evidence of cirrhosis. (E) Image from the patient's flow-FISH study performed on whole-blood lymphocytes, documenting average telomere lengths shorter than the first percentile relative to age-matched controls (image adapted from reference laboratory report; Repeat Diagnostics, North Vancouver, BC, Canada). There was insufficient cellularity to perform additional flow-FISH analysis on the granulocyte lineage. Abbreviation: kb, kilobase(s).

progressively with the age-related sequela of DNA polyploidization,[1] and nuclear size has been demonstrated as an effective method to estimate hepatocyte aging.[2] Though LCC has not been described in STS patients, one group reported hepatocyte anisonucleosis in 2 adults with telomerase complex mutations and liver dysfunction.[3] In our case, the ratio of hepatocytes with LCC was 8-10 times higher than that observed in normal individuals aged 36-40 years and 1.5-2.0 times greater than individuals >85.[1] Macroscopically, the small liver with nodular contours was suspicious for cirrhosis, but only mild fibrosis

was observed on biopsy. Though sampling bias of an underlying cirrhotic liver is possible, it may be that telomere attrition in premature senescence led to global hepatic parenchymal atrophy, similar to a physiological age-related reduction in liver volume.[4]

The patient's aplastic anemia, gray hair, and family history were supportive of an STS. Flow-FISH analysis confirmed abnormally short telomeres for age, and it is possible that the *TERT* VUS identified is causal to the patient's phenotype. It should also be noted that ~40% of patients with shortened telomere lengths do not have an identified variant in telomere-associated genes, attributable to undiscovered telomere protein functions or alternative mechanisms of shortening.[5]

We describe that the combination of prominent histological LCC of hepatocytes in a relatively young patient with a small, but noncirrhotic, liver may suggest an underlying STS. Further studies are required to determine whether hepatocyte LCC and/or reduced liver size are common features of the liver in STS patients.

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Author names in bold designate shared co-first authorship.