Spectrum of Liver Pathology in Dyskeratosis Congenita

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Abstract: Dyskeratosis congenita (DC) is a rare multisystemic disorder associated with defective telomere maintenance. Frequent clinical manifestations of DC include reticular skin pigmentation, dystrophic nails, oral leukoplakia, and bone marrow failure. Hepatic disturbances are reported to occur in 7% of DC patients. This study aimed to evaluate the histopathologic spectrum of hepatic involvement in this disorder. DC patients with liver tissue in the pathology database at Boston Children's Hospital from 1995 to 2022 were identified. Clinical and pathologic information was documented. Thirteen specimens from 11 DC patients were included (M:F = 7:4; median age at the time of liver tissue evaluation: 18 y). DC-associated gene mutations were identified in 9 patients; TERF1-interacting nuclear factor 2 (*TINF2*) was the most frequently represented gene mutation, seen in 4 patients. All patients had bone marrow failure, whereas dystrophic nails, cutaneous abnormal pigmentation, and oral leukoplakia were noted in 73%, 64%, and 55% of patients, respectively. Seven patients underwent bone marrow transplants before biopsy/autopsy (median interval of 45 mo). Histologically, 3 of 4 patients who presented with portal hypertension showed noncirrhotic changes (nodular regenerative hyperplasia and/or obliterative portal venopathy), whereas prominent central and sinusoidal fibrosis was noted in patients with intrahepatic shunting and those showing features of chronic passive congestion. All cases showed hepatocyte anisonucleosis. One patient developed hepatic angiosarcoma, and another 1 had colorectal adenocarcinoma metastatic to the liver. DC patients show heterogeneous histologic findings in their liver. The findings of noncirrhotic portal hypertension, intrahepatic shunting, and angiosarcoma suggest vascular functional/structural pathology as a possible unifying etiology of hepatic manifestations of DC.

Key Words: dyskeratosis congenita, obliterative portal venopathy, nodular regenerative hyperplasia, chronic passive congestion angiosarcoma

(*Am J Surg Pathol* 2023;47:869–877)

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Presented at Society for Pediatric Pathology Spring Meeting in March 2018, Vancouver, BC, Canada.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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In 1910, Zinsser described the first patient with a triad of reticular skin pigmentation, nail dystrophy, and oral leukoplakia.[1] Similar reports by Engman[2] and Cole et al[3] led to the designation of Zinsser-Cole-Engman syndrome, subsequently known as dyskeratosis congenita (DC). DC is now recognized as an inherited multisystemic disorder secondary to defective telomere maintenance, part of a spectrum of genetic telomere biology disorders (TBD). DC patients are at risk to develop bone marrow failure, pulmonary fibrosis, malignancy, and other abnormalities.[4,5] The age of onset, disease phenotype, and severity vary widely between patients. The clinical presentation ranges from minimal syndromic manifestations to severe variants such as Hoyeraal-Hreidarsson syndrome with cerebellar hypoplasia and Revesz syndrome with bilateral exudative retinopathy and intracranial calcifications.[6,7]

Hepatic involvement has been reported to be identified in ~7% of DC patients.[4] Previously reported hepatic manifestations include cirrhosis, hepatocyte necrosis, and hemosiderosis.[4,8,9] However, the literature on these pathologic findings remains limited. In this series, we described the spectrum of liver histopathology in DC patients at our institution.

MATERIALS AND METHODS

DC patients with liver tissue (either biopsy or autopsy specimens) reviewed at Boston Children's Hospital from 1995 to 2022 were identified from the archives of Pathology Department after Institutional Review Board approval. Demographic and clinical information for each patient was documented. Clinical information included genetic alteration, history of bone marrow transplant (BMT), the timing between the liver tissue evaluation in relation to the BMT, liver function tests, clinical manifestations, including the presence of portal hypertension, concurrent medical problems, and the living status. The clinical diagnosis was confirmed by a pediatric hematologist-oncologist (S.A.).

Evaluation of liver enzyme abnormalities (aspartate aminotransferase, alanine aminotransferase, bilirubin, and gamma-glutamyl transferase) was performed on the concurrent laboratory results at the time of biopsy or before the autopsy, when available. The reference range for each patient was determined by the laboratory, where the tests were performed based on the patient's sex and age.

Available histology slides of liver tissue (hematoxylin and eosin, trichrome, iron, and reticulin stains) were reviewed by 2 pathologists (J.P. and A.R.P.) concurrently.

Histologic information on consult cases from external institutions was extracted from pathology reports; the pathology slides were previously evaluated by one of the authors. The histopathologic evaluation included the overall hepatic architecture, degree of inflammation, steatosis and iron deposition, BMT-related changes, and the degree and distribution of fibrosis. Hepatocyte cytologic appearance, particularly the nuclear morphology, was assessed.

Inflammation and fibrosis were reported descriptively (no formal grading and staging systems were utilized). The steatosis was categorized into predominantly macrovesicular (fat globules predominantly occupy the cytoplasm of the hepatocytes and displace the nuclei to the periphery) or microvesicular (small fat droplets without displacement of hepatocyte nuclei). On the basis of its quantity, the steatosis was further classified into minimal (< 5%), mild (5% to 33%), moderate (34% to 66%), or severe (> 66%). The distribution of iron deposition (Kupffer cells and/or hepatocytes) was documented and the degree of accumulation using Perls' Prussian blue stain was graded based on the Scheuer method (grade 0 = no detectable iron; grade 1 = discrete granules recognized at ×40 magnification; grade 2 = discrete granules recognized at ×10 magnification; grade 3 = discrete granules recognized at ×4 magnification; grade 4 = discrete granules recognized at ×1 magnification).

BMT-related changes, including the possibility of graft versus host disease (GVHD) and veno-occlusive disease (VOD) were evaluated. Clinical correlation was performed for diagnostic confirmation. Histologically, GVHD was classified into acute (bile duct injury and endothelialitis with associated portal inflammation) and chronic (bile duct loss with associated cholestasis). Acute VOD was defined by terminal hepatic venules with intimal edema, increased luminal reticulin fibers, striking centrilobular sinusoidal congestion with entrapment of red blood cells, centrilobular hepatocellular necrosis, and deposition of hemosiderin-laden macrophages, whereas chronic disease was marked by occlusion of hepatic venules, dense perivenular fibrosis, and minimal centrilobular congestion.

The existing literature of telomere disorder patients with information on liver histology was reviewed. Selected pathologic findings from these series were compared with our results. We also tried to elucidate if the hepatic pathologic findings were primarily due to DC or were secondary to BMT or if both were contributing factors.

RESULTS

Demographic and Clinical Characteristics

Thirteen liver specimens from 11 DC patients were included in the study. The subjects were 7 male and 4 female, with a median age of 18 years (range: 5 to 39 y) at the time of the first hepatic tissue evaluation. Demographic and clinical information of the patients is summarized in Table 1. Two of the patients (patients 2 and 3) were identical twins. Two patients (patients 1 and 4) had 2 specimens (liver biopsy and liver at the time of autopsy). The overall pathologic material reviewed consisted of 8 liver biopsy specimens and 5 autopsies.

DC-associated gene alterations were identified in 9 patients (82%): 4 TERF1-interacting nuclear factor 2 (*TINF2*), 1 telomerase RNA component (*TERC*), 1 CST telomere replication complex component 1 (*CTC1*), 1 poly (A)-specific ribonuclease (*PARN*), and 1 telomerase reverse transcriptase (*TERT*), 1 regulator of telomere elongation helicase 1 (*RTEL1*). Classic triad of DC was not present in all patients, as abnormal skin pigmentation, dystrophic nails, and oral leukoplakia were identified in 7 (64%), 8 (73%), and 6 (55%) patients, respectively. All patients developed bone marrow failure, and 7 (64%) had undergone BMT before liver tissue evaluation (n = 8 specimens). The median interval between BMT and liver tissue diagnosis was 45 months (range: 2 to 84 mo). In 3 patients, patients 4, 6, and 10, the liver biopsy was acquired without prior BMT. Patient 4 also underwent a postmortem examination.

Pulmonary manifestations of DC (pulmonary fibrosis and pulmonary arteriovenous malformation) were identified in 6 patients (55%). Intrahepatic shunting from portal to hepatic veins was noted in the identical twins (patients 2 and 3) on portography, whereas patients 9 and 10 had splenorenal shunting. Patient 5 developed squamous cell carcinoma of the lip and forehead, while patient 11 had metastatic colorectal adenocarcinoma and oral squamous cell carcinoma. Ten patients (91%) had died at the time of this study.

Hepatic Clinical and Pathologic Features

Four of the 11 patients (36%) presented with portal hypertension. Six of 10 patients (60%) with available concurrent laboratory results demonstrated elevated liver enzyme(s): aspartate aminotransferase (57 to 94 u/L), alanine aminotransferase (50 to 157 u/L), and direct bilirubin (1.6 to 5.6 mg/dL); 4 patients (40%) had normal liver enzymes, and the information was unavailable in 1 patient.

Table 2 highlights the clinical and histologic information of the DC patients. No pathologic evidence of advanced fibrosis or cirrhosis was noted in our patient cohort, including the 4 patients with portal hypertension. Liver specimens in 3 of the 4 patients with portal hypertension (75%) showed histologic changes consistent with noncirrhotic portal hypertension: all had nodular regenerative hyperplasia (NRH), and 1 of them had concurrent obliterative portal venopathy (OPV). The liver biopsy from patient 9 was too limited for a definitive diagnosis. OPV was histologically characterized by densely fibrotic portal tracts with luminal narrowing or obliteration of some or majority of portal vein branches (Figs. 1A, B). NRH was characterized by diffuse hepatic nodularity marked by alternating areas of nodular hepatocellular expansion surrounded by compressed hepatocytic plates without fibrous septum formation (Fig. 1C–F). Patients 1 and 4 demonstrated noncirrhotic

TABLE 1. Demographic and Clinical Information of Patients With Dyskeratosis Congenita

Patient	Sex	Age (y)	Specimen	Genetic mutation(s)	Abnormal skin pigmentation	Dystrophic nail	Oral leukoplakia	BMF	Comorbidities	Prior BMT	BMT liver evaluation interval (months)	Status
1	F	25	Biopsy	Biallelic *CTC1*	+	+	—	+	—	+	2	—
		26	Autopsy	—	—	—	—	—	—	+	19	Deceased
2*	F	5	Biopsy	Het. *TINF2*	+	+	+	+	Portohepatic shunting, pulmonary AVM	+	48	Deceased
3*	F	5	Biopsy	Het. *TINF2*	+	+	+	+	Portohepatic shunting, pulmonary AVM	+	48	Deceased
4	M	21	Biopsy	Biallelic *PARN*	+	+	—	+	Pulmonary AVM, pulmonary fibrosis	—	N/A	—
	—	30	Autopsy	—	—	—	—	—	—	+	84	Deceased
5	F	16	Biopsy	Het. *TINF2*	+	+	+	+	Pulmonary fibrosis, hepatopulmonary syndrome, lip and forehead SCC	+	60	Deceased
6	M	24	Biopsy	Het. *TERC*	—	—	—	+	—	—	NA	Deceased
7	M	18	Autopsy	Unknown	—	+	+	+	Cardiomegaly with biventricular hypertrophy, pulmonary fibrosis	+	7	Deceased
8	M	20	Autopsy	Het. *TERT*	—	—	—	+	Hepatic angiosarcoma	—	NA	Deceased
9	M	13	Biopsy	Het. *TINF2*	+	+	+	+	Splenorenal shunting, GI bleeding	+	42	Deceased
10	M	17	Biopsy	Unknown	—	—	—	+	Splenorenal shunting, pulmonary AVM	—	N/A	Living
11	M	39	Autopsy	Biallelic *RTEL1*	+	+	+	+	Metastatic colorectal adenocarcinoma, oral SCC	—	NA	Deceased

* Identical twins.
AVM indicates arteriovenous malformation; BMF, bone marrow failure; CTC1, CST telomere replication complex component 1; F, female; GI, gastrointestinal; Het, heterozygous; M, male; NA, not applicable; SCC, squamous cell carcinoma.

portal hypertensive findings in both their liver biopsy and autopsy specimens.

The abnormal liver enzyme(s) seen in 6 patients did not correlate with significant portal and/or lobular inflammation. Only minimal portal inflammation was identified in 2 of 13 specimens (15%), characterized by predominantly lymphocytic infiltrates. Steatosis was noted in 4 of 13 specimens (31%; 3 mild and 1 moderate); all showed predominantly macrovesicular steatosis. Iron deposition (Fig. 2A) was identified in 9 specimens (69%) from 8 patients (73%). Most of the cases (7 of 9; 78%) showed moderate to severe iron accumulation (3+ to 4+) in both hepatocytes and reticuloendothelial cells. Hepatocyte anisonucleosis, characterized by nuclear hepatocellular enlargement with hyperchromasia and mild pleomorphism (Fig. 2B), was identified in all patients (100%).

Histologic features of chronic passive congestion, including sinusoidal dilatation (Fig. 2C) with or without perivenular and perisinusoidal fibrosis (Fig. 2D), were seen in 7 specimens (54%) from 6 patients (55%) who had intrahepatic shunting from portal to hepatic venis and/or cardiopulmonary manifestations. Bile duct injury (Fig. 2E) was identified in patients 5 and 9; although these samples were taken after BMT, the interval to liver biopsy was several years, and in the absence of clinical manifestations of GVHD. Patient 7 showed narrowing central veins with intimal thickening (Fig. 2F).

Patient 8 presented with and subsequently died from intraperitoneal bleeding secondary to diffuse hepatic lesions (Figs. 3A, B). Histologically, these lesions were characterized by highly atypical cells with epithelioid morphology and vascular lumen formation (Fig. 3C). Foci of peliotic changes were noted. The neoplastic cells were immunoreactive for vascular markers (Fig. 3D), while negative for GLUT-1 and D240 immunohistochemistry. The pathologic findings were characteristic of hepatic angiosarcoma. There were no pathologic findings to suggest a benign precursor lesion (eg, hemangioma). Postmortem examination of patient 11 confirmed metastatic colorectal adenocarcinoma to the liver (Fig. 3F).

Liver Pathology of Patients With TBDs in the Literature

Two previous case series with detailed information on liver histology in TBD patients were reviewed for

TABLE 2. Hepatic Manifestations of Dyskeratosis Congenita

Case	Abnormal liver enzymes	Portal hypertension (clinical)	Portal inflammation	Lobular inflammation	Steatosis	Fibrosis	Iron deposition	Hepatocyte anisonucleosis	Bile duct injury	Others
1a	↑DB (2.9)	+	—	—	—	Focal sinusoidal	3+ (h,r)	+	—	NRH and OPV
1b	↑DB (5.6)	+	Minimal	—	Moderate	Portal, periportal	3+ (h,r)	+	—	NRH and OPV
2	↑AST (57)	—	—	—	—	Pericentral, sinusoidal	—	+	—	CPC
3	↑AST (58)	—	—	—	—	Pericentral, sinusoidal	—	+	—	CPC
4a	Normal	+	—	—	Mild	—	3+ (h,r)	+	—	NRH and CPC
4b	Normal	+	—	—	—	—	—	+	—	NRH and CPC
5	↑AST (85) ↑ALT (72) ↑DB (1.6)	—	—	—	—	Portal, periportal	3+ (h,r)	+	+	CPC
6	Normal	—	—	—	Mild	-	4+ (h,r)	+	—	—
7	↑AST (93) ↑ALT (157) ↑DB (2.9)	—	—	—	—	Pericentral, sinusoidal	3+ (h,r)	+	—	CPC, narrowing central veins with intimal thickening
8	Unavailable	—	—	—	—	—	1+ (r)	+	—	Hepatic angiosarcoma
9	Normal	+	Minimal	—	Mild	-	2+ (r)	+	+	—
10	Normal	+	—	—	—	Portal, sinusoidal	—	+	—	NRH and CPC
11	↑AST (94) ↑ALT (50) ↑DB (1.8)	—	—	—	—	—	3+ (h,r)	+	—	Metastatic colorectal adenocarcinoma

ALT indicates alanine aminotransferase (u/L); AST, aspartate aminotransferase (u/L); CPC, chronic passive congestion; DB, direct bilirubin (mg/dL); h, hepatocyte iron deposition; NRH, nodular regenerative hyperplasia; r, reticuloendothelial (Kupffer cell) iron deposition.

comparison;[8,9] the findings are summarized in Table 3. Calado et al[8] provided data of individuals with familial telomerase mutations (liver histology was available in 7 patients of 4 unrelated families; median age: 46 y; range 20 to 57 y). The series from Gorgy et al[9] included TBD patients with hepatopulmonary syndrome (liver histology was available in 6 patients; median age: 37 y; range 17 to 53 y). There was no information regarding the BMT status of these 13 patients.[8,9]

Both studies demonstrated a subset of patients whose hepatic tissue showed features of OPV and NRH; the latter was identified in 67% of patients with hepatopulmonary syndrome. Similar to our findings, portal inflammation, and steatosis were identified in a small subset of patients. Advanced fibrosis was identified in 2 patients with familial telomerase mutations (1 bridging fibrosis and 1 cirrhosis).[8] Iron accumulation and hepatocellular nuclear pleomorphism were only seen in a subset of patients. Features of chronic passive congestion were noted in 1 patient with hepatopulmonary syndrome.[9]

DISCUSSION

Our series demonstrates the broad spectrum of liver pathology in DC patients ranging from noncirrhotic portal hypertension (OPV and NRH), chronic passive congestion, hemosiderosis, hepatocellular nuclear enlargement with pleomorphism and hyperchromatism, and malignancy (primary hepatic angiosarcoma and metastatic colorectal adenocarcinoma). These findings underline the complex nature of liver disease in patients with DC.

Although advanced hepatic fibrosis has been described in DC patients, none of our patients showed evidence of bridging fibrosis or cirrhosis.[4,8,10] Instead, noncirrhotic histologic abnormalities were identified in 3 DC patients who presented with portal hypertension (patient 1, patient 4, and patient 10). These findings confirm previously reported observations.[8,9] Gorgy et al reported NRH in 4 of 6 patients with telomere disorders (67%); the relatively high proportion might be explained by selection bias (the study exclusively assessed patients with hepatopulmonary syndrome).[9] They further reported that patients with telomere-mediated hepatopulmonary syndrome and noncirrhotic portal hypertension demonstrated progressive phenotypes, as these patients eventually succumbed to complications of hypoxia and portal hypertension.[9]

Noncirrhotic portal hypertension is an umbrella term for heterogeneous conditions showing portal hypertension in the absence of cirrhosis. It has been associated with infiltrative diseases, vascular disorders, schistosomiasis, congenital hepatic fibrosis, and sarcoidosis.[11] If no clear etiology is identified, the diagnosis of idiopathic noncirrhotic portal hypertension can be rendered. The histopathologic features of noncirrhotic portal hypertension are subtle, of variable severity and often unevenly distributed; thus, the diagnosis is not always straightforward. The histologic findings may include OPV, NRH, lobular lesions (eg, sinusoidal dilatation and perisinusoidal fibrosis), and incomplete septal cirrhosis.[12]

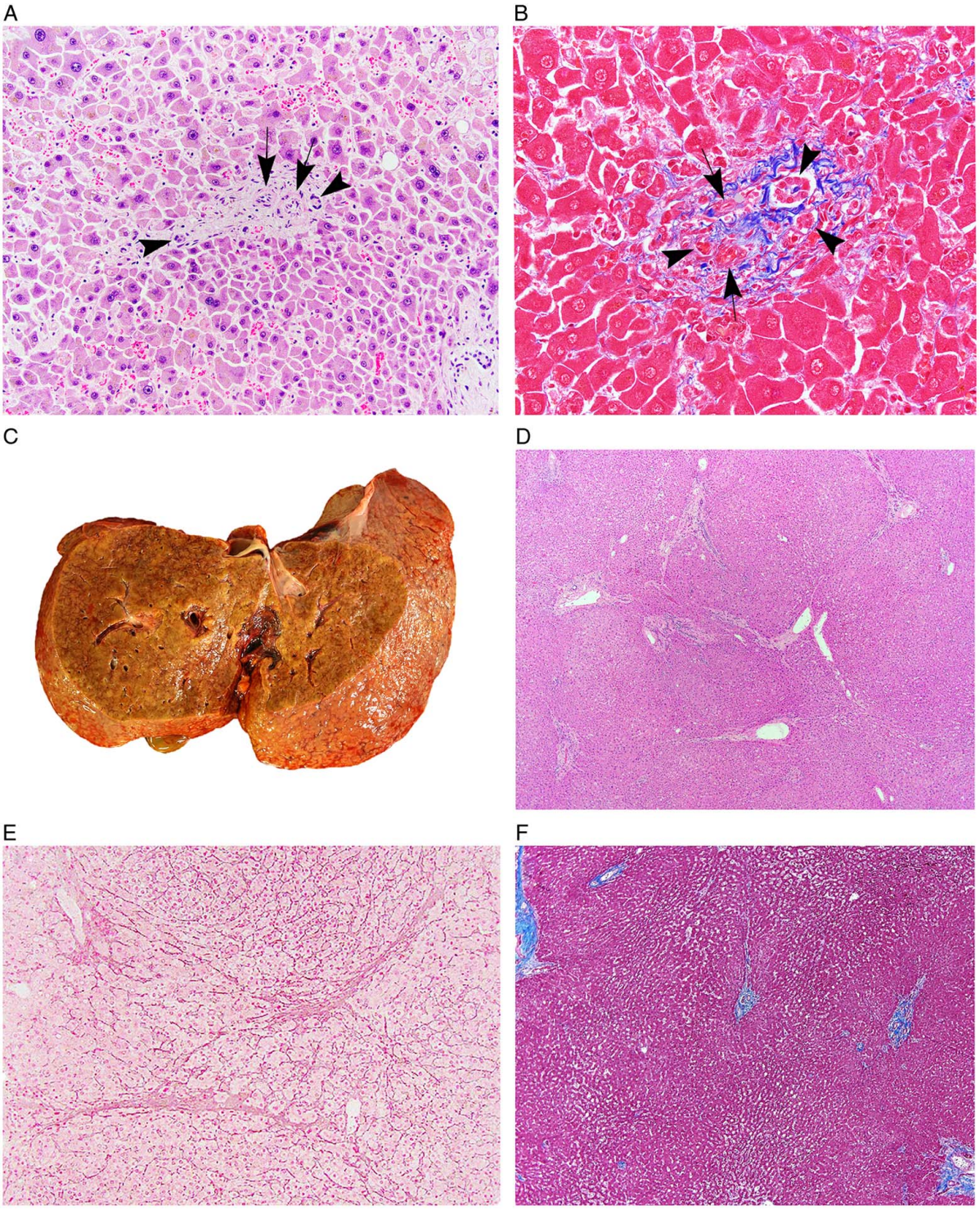

FIGURE 1. A and B, The liver specimen of patient 1, who presented with portal hypertension, demonstrated features of obliterative portal venopathy, characterized by sclerotic portal tracts with obliterated portal veins. Interlobular bile ducts (arrowheads) and hepatic artery (arrows) were consistently present, while portal veins were not evident (A) (hematoxylin and eosin and Masson trichrome stains). C, Postmortem examination of patient 4 revealed liver with a nodular cut surface. D–F, Histology showed nodular liver with alternating areas of hypertrophic and compressed atrophic hepatocytes without evidence of fibrosis (hematoxylin and eosin, reticulin, and Masson trichrome stains). The findings were those of nodular regenerative hyperplasia.

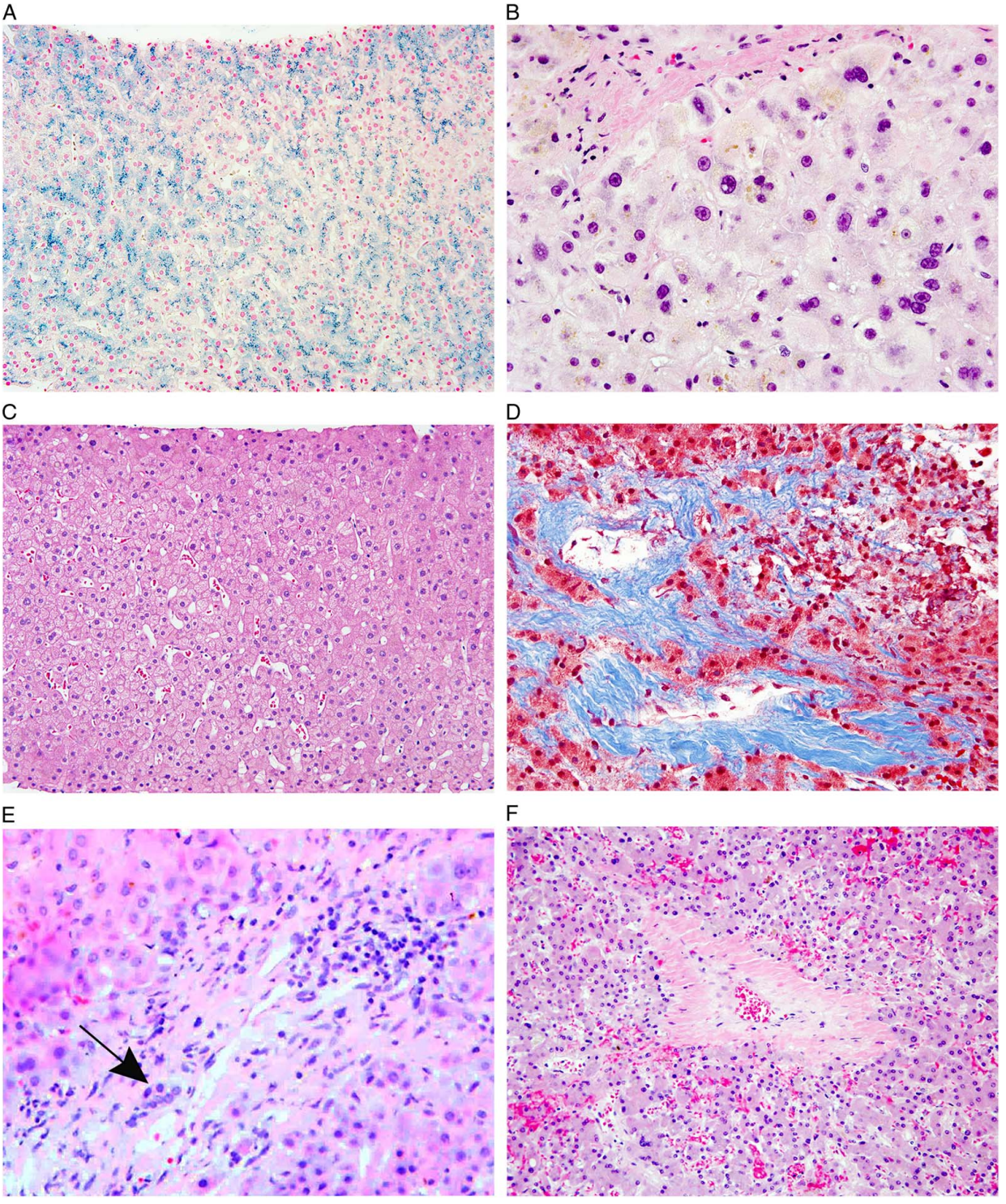

FIGURE 2. A, Iron deposition (hemosiderosis) in the hepatocytes and/or reticuloendothelial cells was noted in 8 patients (Iron stain), while hepatic anisonucleosis (hematoxylin and eosin [H&E] stain) was identified in all patients (B). C, Sinusoidal dilatation was seen in the liver biopsy of patient 7 who had pulmonary fibrosis (H&E stain). D, Perivenular and sinusoidal fibrosis was noted in patient 2 who presented with intrahepatic shunting (Masson trichrome stain). E, Bile duct injury (arrow) was noted in patient 5; the finding was of unknown significance (H&E stain). F, Patient 7 showed intimal thickening of the central vein with centrilobular sinusoidal congestion (H&E stain).

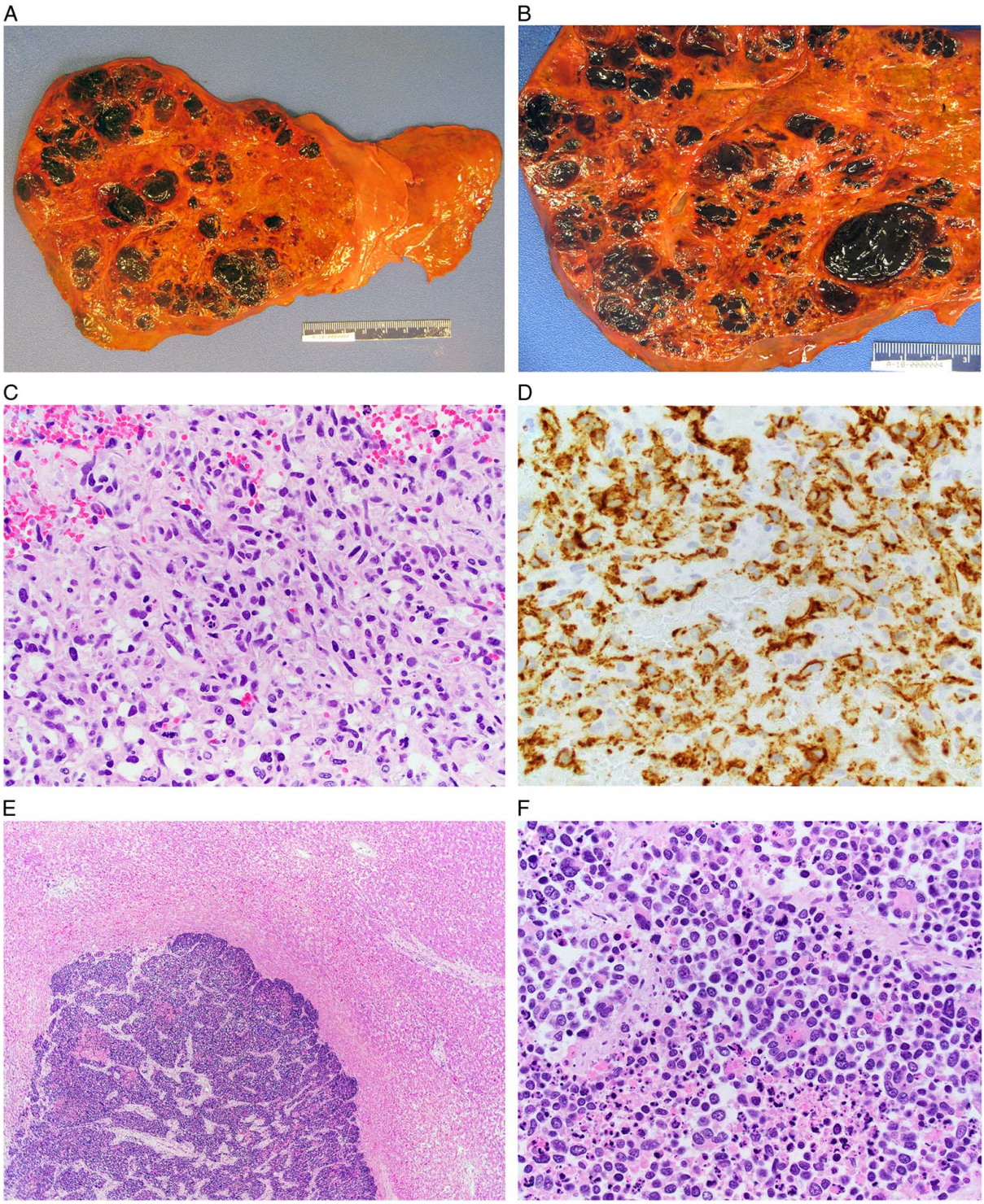

FIGURE 3. A and B, Postmortem examination of patient 8 revealed multifocal hemorrhagic nodules in the liver. C, Histologically, these lesions were characterized by sheets of highly atypical cells showing endothelial differentiation (hematoxylin and eosin stain); the neoplastic cells were diffusely immunoreactive for CD31 (D). The findings were in keeping with a hepatic angiosarcoma. E and F, Patient 11 with metastatic colorectal adenocarcinoma (poorly differentiated), characterized by discohesive atypical cells and associated necrosis (hematoxylin and eosin stain).

TABLE 3. Liver Pathology of Patients With Telomere Disorders in the Current Study and Previous Series

	Current study	Calado et al[8]	Gorgy et al[9]
Patients	11	7	6
Age (median; range in y)	18 (5-39)	46 (20-57)	37 (17-53)
Previous BMT, n (%)	7 (64)*	Not provided	Not provided
NRH, n (%)	3 (27)	2 (29)	4 (67)
OPV, n (%)	1 (9)	1 (14)	1 (17)
Portal inflammation, n (%)	2 (18)	2 (29)	2 (33)
Steatosis, n (%)	4 (36)	1 (14)	1 (17)
Fibrosis, n (%)	3 (27) mild portal/periportal 4 (36) pericentral/sinusoidal	1 (14) – mild portal/periportal 1 (14) – bridging fibrosis 1 (14) – cirrhosis with extensive sinusoidal fibrosis	1 (17) minimal portal/periportal
Iron accumulation, n (%)	8 (73)	2 (29)	3 (50)
Anisonucleosis, n (%)	11 (100)	2 (29)	Not provided
Chronic passive congestion, n (%)	6 (55)	0	1 (17)

*See Table 1 for details.
BMT = Bone marrow transplant; NRH = nodular regenerative hyperplasia; OPV = obliterative portal venopathy.

OPV is characterized by portal vein obliteration/stenosis, herniated portal veins, hypervascularized portal tracts, and periportal abnormal vessels histologically.[13] It has been associated with genetic predisposition, bacterial and HIV infections, medication adverse effects, and autoimmune conditions such as systemic lupus erythematosus, celiac disease, and mixed connective tissue disorder.[14] However, the mechanism of OPV is unclear. This entity is occasionally seen concurrently with another form of noncirrhotic portal hypertension, NRH. NRH is characterized by nodular hyperplasia of hepatocytes, which are arranged in more than 2 cell-thick plates, while the surrounding parenchyma is compressed and atrophic. NRH has been associated with post-BMT patients as the immunosuppressive agents are thought to be potentially damaging to the endothelial cells of small hepatic veins.[15,16] NRH is also seen with increasing age in the general population.[17] Although it can be difficult to determine whether OPV and NRH due to DC versus secondary to BMT, our findings support the hypothesis that noncirrhotic portal hypertension is a primary manifestation of DC. In our study, patient 1 had developed portal hypertension years before BMT, and the pre-BMT liver biopsies of patients 4 and 10 also showed findings consistent with NRH.

Portal and periportal fibrosis were identified in a small number of our patients (27%); meanwhile, pericentral and sinusoidal fibrosis was seen in 4 (36%) who concurrently showed features of chronic passive congestion. In contrast to our study, Calado et al[8] reported advanced fibrosis in 2 of 7 patients (29%). This could be explained by the distinct patient characteristics between the 2 studies; our cohort consisted of children and young adults (median age: 18 y), whereas Calado and colleagues evaluated adults (median age: 46 y) with familial TBD. The 2 patients with advanced fibrosis reported by Calado et al[8] were a 48-year-old woman (bridging fibrosis) and a 57-year-old man (cirrhosis) from unrelated families. Rocha et al[18] also reported an 18-year-old male who developed cirrhosis 8 years after BMT.

Minimal portal lymphocytic inflammation and mild-to-moderate steatosis were identified in 18% and 36% of the patients, respectively. These findings are often nonspecific, with no obvious correlation with abnormal liver enzymes or fibrosis, and the small number of cases precludes statistical analysis. Pathologic findings reported by other case series but not identified in the current study include massive hepatocyte necrosis, lobular inflammation dominated by plasma cells, bile duct paucity, diffuse cholestasis, and noncaseating granulomas.[8,9] Comorbidities, such as autoimmune hepatitis, cholangiopathies, and drug-related reaction, could not be entirely excluded in those series.

Approximately 85% of DC patients develop bone marrow failure and subsequently require multiple blood transfusions.[4] This may lead to increased iron deposition (hemosiderosis), which usually starts in the sinusoidal Kupffer cells and is eventually seen in the hepatocytes. Patient 4, however, developed hemosiderosis in hepatocytes and reticuloendothelial cells before receiving red blood cell transfusions. This observation raises the possibility of endothelial damage (microvascular injury) as a contributing factor to hemosiderosis in DC patients.

Hepatic anisonucleosis, marked by varying nuclear size and shape, is usually encountered in the liver of older patients. This histologic feature was consistently found in our DC patient cohort and thus may reflect "premature aging" or sequelae of regenerative exhaustion secondary to defective telomere maintenance. We have observed similar nuclear changes in ataxia telangiectasia, another disorder with a defective DNA repair.

Histologic features of chronic passive congestion were consistently seen in 6 patients who had cardiopulmonary manifestations of DC and intrahepatic shunting from portal to hepatic veins. Recognized pulmonary phenotypes of DC include pulmonary fibrosis and pulmonary microvascular shunting.[19] In addition, one of the patients had cardiomegaly with biventricular hypertrophy, which might contribute to the findings of chronic passive congestion. Pericentral and sinusoidal fibrosis was identified in 4 of the 6 patients (67%), underscoring the chronic nature of these histologic changes.

We noted bile duct injury in 2 patients. Although these patients underwent BMT before hepatic tissue evaluation, there was no histologic evidence of endothelialitis, and the clinical findings were not in keeping with GVHD. Thus, the significance of bile duct injury in these patients is unclear. Other BMT-related pathologic findings, such as VOD, drug-induced liver injury, and opportunistic infections, were not identified in our patient cohort.

One of our patients died from hepatic angiosarcoma, which has been described in young patients with DC.[20,21] Olson et al[20] reported a 17-year-old male patient who developed fatal hepatic failure caused by an aggressive, infiltrating angiosarcoma, whereas Horiguchi et al[21] described a 23-year-old male patient who died 4 months after diagnosis with hepatic angiosarcoma due to tumor progression and disseminated intravascular coagulation. DC is considered as a cancer predisposition syndrome because of genome instability secondary to disruption of telomere maintenance. The morphologic patterns of hepatic angiosarcoma in DC include spindled[21] and epithelioid morphology with cavernous/peliotic changes.[20] Rare cases of malignant transformation from infantile hemangioma to hepatic angiosarcoma have been reported.[22,23] In the experience of one of the authors (A.R.P.), a benign hemangioma *NOS* component is not uncommonly present in pediatric hepatic angiosarcoma. None of the reported hepatic angiosarcoma cases in DC (including our case) showed pathologic evidence of a precursor lesion.[20,21] Although the pathogenesis of angiosarcoma in DC patients remains uncertain, the association of hepatic vascular abnormalities with DC suggests angiosarcoma may be a rare endpoint of endothelial cell dysfunction caused by critically short telomeres.

Our study is limited by its retrospective nature and incomplete information, as some cases were sent from other institutions for an expert consultation. In addition, genotype-phenotype statistic correlation is not possible because of the low number of patients.

In summary, we described the heterogeneous liver histopathology in DC patients. Pathologists should be aware of the histopathologic spectrum in the liver associated with different pulmonary manifestations, bone marrow failure, and BMT-related complications. Although our findings corroborate the results of prior studies,[8,9] we reported a higher proportion of patients with hepatic anisonucleosis (100%) and changes of chronic passive congestion (54.5%). Moreover, the findings of intrahepatic vascular shunting, noncirrhotic portal hypertension, and angiosarcoma, suggest the possibility of vascular structural/functional problems as a mechanism of hepatic manifestations in these patients. These results expand the phenotypic spectrum of vascular complications in DC patients, which include retinal vessel abnormalities, avascular necrosis, and gastrointestinal telangiectatic anomalies.[24]

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