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Pulmonary Arteriovenous Malformations: an uncharacterized phenotype of Dyskeratosis Congenita and related Telomere Biology Disorders

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Abstract

Pulmonary arteriovenous malformations are under-recognized in telomere biology disorders and present diagnostic and therapeutic challenges.

Keywords

Dyskeratosis congenita; pulmonary arteriovenous malformation; telomere; hepatopulmonary syndrome

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To the Editor

The telomere biology disorder (TBD), dyskeratosis congenita (DC), is a multi-system inherited bone marrow failure syndrome and cancer predisposition syndrome caused by germline mutations in telomere biology genes (*DKC1, TINF2, TERC, TERT, NOP10, NHP2, CTC1, WRAP53, ACD, RTEL1* and *PARN*). The classic triad of reticular skin pigmentation, dysplastic nails, and oral leukoplakia is diagnostic of DC.[1, 2] Leukocyte telomere lengths less than the first percentile for age measured by flow cytometry with fluorescence *in situ* hybridization (flow FISH) are consistent with DC in the presence of other phenotypic features.[3] Pulmonary fibrosis (PF), a known complication of DC/TBD, occurs in at least 20% of patients.[1] Pulmonary arteriovenous malformations (PAVMs) in DC have been previously described in case reports or small case series in the context of hepatopulmonary syndrome (HPS).[4–9] Presenting features of PAVMs may overlap with those of PF including dyspnoea, orthopnoea, platypnea, cyanosis and digital clubbing. HPS is described as pulmonary vascular dilatation due to liver disease of any cause (cirrhotic/non-cirrhotic with/without portal hypertension), leading to deficient arterial oxygenation.[10]

This multi-institutional, retrospective, medical record review evaluated patients diagnosed with both DC/TBD and PAVMs. All participants were enrolled in an Institutional Review Board (IRB) approved study at the primary reporting institution. Data were received and maintained at the National Cancer Institute (NCI) within the IRB-approved Inherited Bone Marrow Failure Syndromes (IBMFS) protocol (NCI 02-C-0052, NCT 00027274).[11] The study includes patients of any age, gender and race who were diagnosed with DC/TBD based on clinical criteria and/or genetic testing positive for a known disease-causing mutation.

We report 13 unrelated patients with both DC/TBD and PAVM. Median age at diagnosis of DC/TBD was 13 years (range 1–27 years), that of PAVMs was 15 years (range 3–32 years). The male:female ratio was 7:6. The majority (77%) were of European ancestry. Six patients (46%) had germline mutations in *TINF2* (Table 1). One patient did not have a known causative gene mutation. Data on clinical manifestations at the time of DC/TBD diagnosis were available on 12 patients and are detailed in Table 1. Ten (83%) patients had at least one feature of the mucocutaneous triad, all tested patients had very short telomere length for age, and six (50%) had aplastic anaemia (AA). Ten of 13 (77%) patients underwent haematopoietic cell transplant (HCT) at median age 6 years (range 1–21 years).

The clinical details of PAVM diagnosis and management are also shown in Table 1. Two of 13 (15%) patients had PAVMS diagnosed prior to their diagnosis of DC. Nine of 10 (90%) patients who underwent HCT had PAVMs diagnosed at a median time interval of 5 years (range 2–8 years) after HCT. Notably, two asymptomatic patients had PAVMs diagnosed after evaluation of an unexplained decrease in DLCO. Six patients (46%) had PF confirmed by computerized tomography (CT) scan around the time of their PAVM diagnosis. DLCO was reduced (16–56% of predicted) out of proportion to other pulmonary function tests (PFTs) and to the radiologic extent of PF when present. Transthoracic contrast echocardiography with agitated saline bubble contrast (TTCE) was indicative of a delayed

right-to-left shunt (contrast appearing in left heart 3 or more beats after right heart) in 10 of 11 patients (91%) who underwent TTCE. Two patients who did not undergo TTCE had PAVMs confirmed by abnormal radioisotope lung perfusion scan and/or cardiac catheterization. Five patients underwent lung perfusion scans that confirmed the presence of right-to-left shunting with tracer uptake in the brain and/or kidney, including the patient with a negative TTCE. Intrapulmonary shunt assessment done by arterial blood gases at sea level in one patient showed decreased shunting from sitting-upright (PaO2 of 32 mm Hg on room air and 102 mm Hg on 100% oxygen- 32.8% shunt) to supine posture (PaO2 of 247 mm Hg on 100% oxygen -21.8% shunt) in concordance with his orthodeoxia and platypnea. Only Patient 5 had PAVMs visible by CT scan and underwent coiling of the same. Her clinical course was complicated by development of a brain abscess three months after coiling, attributed to a bacterial embolus consequent to right-to-left shunting. The remaining patients had very small or microscopic PAVMs that were not amenable to transcatheter embolization. Importantly, nine of 13 (69%) patients did not have laboratory or radiological evidence of liver disease at the time of PAVM diagnosis.

In summary, this case series establishes PAVMs as a clinically important pulmonary phenotype in DC/TBD and one that may occur in the absence of overt HPS, in the absence of symptoms, and in patients of any age, genotype or phenotype (Table 1). The mechanism underlying development of vascular malformations in patients with aberrant telomere biology is not known. Vascular complications previously reported in DC/TBD have only recently been described as phenotypic features of the DC/TBD spectrum, such as in Revesz syndrome and Coats' plus.[1,9] Further research is needed to determine whether PAVMs are a consequence of telomere dysfunction; are associated with TGF-beta signalling pathways similar to hereditary haemorrhagic telangiectasia (HHT),[12] an autosomal dominant disease of abnormal angiogenesis; and if any association exists between HCT and PAVMs in DC/TBD.

Timely and accurate diagnosis of PAVMs in DC/TBD is essential for appropriate clinical care and prevention of life-threatening complications (e.g., transient ischemic attacks, stroke, or brain abscesses) caused by paradoxical embolism in the setting of a right-to-left shunt. Multiple diagnostic modalities may be used for the detection of PAVMs including TTCE, DLCO, 6-minute walk test, and quantification of abnormal physiological shunting by arterial blood gases at sea level. Of these, TTCE is the most sensitive (close to 100% sensitivity reported in HHT).[13] While PFTs are non-specific, isolated decrease in DLCO may indicate abnormal shunting, warranting evaluation for occult PAVMs.[14]

This case series reports nine patients with DC/TBD who developed PAVMs in the absence of overt HPS. However, it is not clear whether HPS and PAVMs occur along a continuum as components of one disorder or whether PAVMS can occur without concurrent or future development of liver disease.[10] With no known curative medical treatment options for PAVMs not amenable to transcatheter embolization, clinicians need to be aware of the therapeutic challenges of PAVMs. Anecdotal reports of agents including nifedipine and danazol among others have been inconsistent with respect to improvement of symptoms. Lung transplantation, which is an option for PAVMs not surgically treatable, would be

unsuccessful if HPS was the underlying cause. In that instance, liver transplantation would be considered and is associated with significant mortality and morbidity.[15]

In conclusion, PAVMs are a pulmonary phenotype of DC/TBD that may occur independently of HPS, in asymptomatic patients, across any phenotypic or genotypic presentation. The NCI's IBMFS study includes 145 affected DC patients, of whom 5 (3%) were symptomatic of and diagnosed with PAVMs and are included here.[11] We expect that the prevalence of PAVMs in DC/TBD will likely be higher with formal evaluation of PAVMs across all patients since PAVMs can occur in the absence of symptoms. Isolated decrease in DLCO and/or hypoxia in DC patients warrant further investigation for PAVMs including TTCE, lung perfusion scan, and evaluation of intrapulmonary shunting. Further research on the underlying biological mechanisms, including the pathophysiologic relationship between PAVMs and HPS, and therapeutic options are needed to be able to better manage and treat these patients.

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TABLE 1

Clinical, laboratory and management details of DC and PAVMs in study participants

Patient	At DC/TBD Diagnosis			Telomere length	Gene, mutation	AA Treatment	HCT indication	Age at HCT	HCT prep, GVHD prophylaxis	At PAVM Diagnosis						Age at last follow-up
	Age	Features of DC triad	AA							Age	Presentation	DLCO (%predicted)	Co-existent PF	Positive TTCE	Evidence of liver disease	
1	13	L	Mild	VL	*TERT*, c.2266C>T p. R756C	Oxymetholone, danazol	N/A	N/A	N/A	15	Cyanosis, hypoxia, clubbing	16	Y	Y	N	25
2	27	None	Moderate	VL *	*RTEL1*, c.2227G>A p.D734N + c.2684C>T p.P895L	Danazol	N/A	N/A	N/A	32	None	52	N	Y	N	32
3	21	None	Moderate	VL *	*TERT, c.994G>A* p.1062A>T+ c.844T>C p. S795P	Danazol	N/A	N/A	N/A	27	No symptoms, clubbing	53	N	Y	Hepatic fibrosis, splenomegaly, portal HTN	27
4 NCI 291-1	18	S, N	Moderate	VL	*Compound het. PARN* c.19A>C p.N7H; gene deletion	HCT	Severe thrombocytopenia **	21	Flu/Alem, CSA/MMF	21	Dyspnoea on exertion, clubbing	28	Y	Y	N	24
5 NCI 216-1	8	N, L	Severe	VL	UNK	HCT	AA	9	Flu/Bu/CPM/ATG, Tacro/ T cell depletion	14	Dyspnoea on exertion	50	Y	Y	N	17
6 NCI 440-1	3.5	S, N	Severe	VL	*DKC1*, c.1223C>T p.T408I	ATG/CSA, Androgen, G-CSF, Darbepoetin, HCT	AA	7	Flu/CPM/ATG, CSA/MMF	12	Dyspnoea, clubbing	48	N	N/A	N	14
7	17	S, N, L	None	N/A	*TINF2*	HCT	MDS	5	TBI, CSA/MTX	13	Hypoxia, dyspnoea on exertion, clubbing	18	N	Y	N	d.19
8 NCI 297-2	16	S, N, L	Severe	VL	*RTEL1*, c.3361delG p.A1121LfsX6, c.1338+3 A>G IVS15+3 A>G	HCT	AA	19	Flu/CPM/ Alem/TBI, Tacro/MMF	22	Dyspnoea	56	Y	Y	Mild hepatic fibrosis, Portal HTN	22
9 NCI 349-1	5.5	S, N, L	Severe	VL	*TINF2*, c.845G>A, p.R282H	HCT	AA	5.7	Flu/CPM/Alem/TBI, CSA/MMF	12	Dyspnoea, cough	N/A	Y	N/A	N	d. 13
10	N/A	N/A	N/A	N/A	*TINF2*, c.845G>A, p.R282H	HCT	AA	2.9	Flu/Alem/CPM/Anti CD-45, CSA/MMF	7	Hypoxia	N/A	N	Y	N	10
11	4	S, N, L	Moderate	VL	*TINF2*, c.805C>T, p.Q269X	HCT	AA	4.7	Flu/Alem/Anti-CD45, Tacro	10	Progressive dyspnoea	N/A	Y	Y	Mild hepatic fibrosis, splenomegaly, portal HTN	11
12 NCI 145-1	9	S, N	Severe	VL	*TINF2*, c.844C>A p.R282S	HCT	AA	10.8	Flu/Bu/CPM/ATG, Tacro/T-cell depletion	15	Dyspnoea on exertion	37	N	N	Hepatic fibrosis, s/p splenectomy	d. 16
13 NCI 438-1	1	N	Severe	VL	*TINF2*, c.844C>A p.R282S,	HCT	AA	1.5	Flu/CPM/ATG, CSA	3	Chronic hypoxia	N/A	N	Y	N	d. 4

Abbreviations: DC: Dyskeratosis congenita; TBD: telomere biology disorder; PAVM: Pulmonary arteriovenous malformation; S: Skin pigmentation; N: Dysplastic nails; L: Oral leukoplakia; AA: Aplastic anaemia; VL: Telomere length “very low”, < 1st percentile for age in all leukocyte subsets measured by Flow cytometry and fluorescence *in situ* hybridization (unless indicated by *); UNK: Causative gene unknown; HCT: Hematopoietic stem cell transplantation; ATG: Anti-thymocyte globulin; CSA: Cyclosporin; G-CSF: granulocyte colony stimulating factor; MDS: myelodysplastic syndrome; GVHD: graft versus host disease; Flu: Fludarabine; Alem; Alemtuzamab; MMF: mycophenolate mofetil; Bu: Busulfan; CPM: cyclophosphamide; Tacro: Tacrolimus ; MTX: Methotrexate; TBI: Total body irradiation; N/A: not available/ not applicable; DLCO: Diffusion lung capacity of carbon monoxide; PF: pulmonary fibrosis; TTCE: Transthoracic contrast echocardiogram; HTN: hypertension; s/p: status-post; Y: Yes; N: No

*: telomere length < 1st percentile for age measured by qPCR;

**: HCT for severe thrombocytopenia that was precluding candidacy for lung transplant

Age in years. d.: died