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ORIGINAL ARTICLE

Spontaneous pneumothorax and hemothorax frequently precede the arterial and intestinal complications of vascular Ehlers–Danlos syndrome

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Vascular Ehlers–Danlos syndrome (vEDS) is a connective tissue disorder due to defective type III collagen production and is associated with arterial rupture, spontaneous intestinal perforation, and gravid uterine rupture. Spontaneous pneumothorax and/or hemothorax (P/HTX) also occurs in vEDS patients. The temporal relation of pulmonary manifestations to arterial and intestinal complications in vEDS has not been well described. This was investigated in a multi-institutional retrospective case series of vEDS patients with confirmatory testing for *COL3A1* mutation between 2000 and 2012. Data abstracted included demographics, family histories, presentation, and management of associated complications. Ninety-six cases (39% males, mean age 38.6 ± 15.5 years, range 8–79) had confirmatory testing for vEDS. P/HTX was documented in 17 (17.7%) cases. Most P/HTX preceded the diagnosis of vEDS (81%). Diagnosis of vEDS was made after arterial or intestinal complications at a mean of 7 years (range 0–26) post the initial P/HTX. In conclusion, spontaneous P/HTX is an early manifestation of vEDS frequently preceding an arterial complication or intestinal perforation. Thus, a spontaneous P/HTX in a young patient should trigger a differential diagnosis that includes vEDS. This should lead to an investigation of other vEDS features and subsequent genetic testing if vEDS features are present.

KEYWORDS

Ehlers–Danlos syndrome type IV, spontaneous pneumothorax, spontaneous hemothorax, type III collagen, vascular Ehlers–Danlos syndrome

1 | INTRODUCTION

Vascular Ehlers–Danlos syndrome (vEDS) also known as Ehlers–Danlos Syndrome type IV (EDS IV: MIM 130050) is an autosomal dominant connective tissue disorder characterized by translucent skin that bruises easily and arterial complications (arterial aneurysms, dissection, or rupture), spontaneous intestinal perforation, and gravid uterine rupture (Byers et al., 2017; Malfait et al., 2017; Pepin, Murray, & Byers, 1993). The diagnosis of vEDS is based on clinical criteria as detailed by the revised Nosology of Villefranche and confirmed by identification of a pathogenic variant in the gene for *COL3A1* and in rare conditions a pathogenic variant in *COL1A1* (Malfait et al., 2017). Pneumothorax (PTX) and hemothorax (HTX) are also manifestations of vEDS and are considered one of the "minor" diagnostic criteria (Malfait et al., 2017). Spontaneous and/or recurrent pneumothoraces and hemothorax (P/HTX) are often in association with pulmonary blebs, cystic lesions, and hemorrhagic or fibrous nodules and are rare in the general population with an estimate of 0.01% of the population (Ayres, Pope, Reidy, & Clark, 1985; Dowton, Pincott, & Demmer, 1996; Hatake et al., 2013; Ishiguro et al., 2009; Murray et al., 1995; Purohit, Marsland, Roberts, & Townsend, 2009; Yost, Vogelsang, & Lie, 2014). In this report, we describe the prevalence of pulmonary complications in a contemporary cohort of patients with confirmatory genetic testing vEDS and highlight the temporal relation of these complications to the occurrence of arterial and intestinal complications.

2 | METHODS

This is a multicenter cross-sectional retrospective case series of patients with genetic testing for vEDS showing pathogenic variants in *COL3A1* between 2000 and 2012. The study was approved by the Institutional Review Board at the University Texas Health Science Center at Houston McGovern Medical School and the National Institute on Aging, (NCT00270686, MedStar IRB #2003–086). Data collection was initially retrospective and had longitudinal follow-up from the date of enrollment spanning a 12-year period ending on January 3, 2013. Data were obtained from study visits, review of available medical records, correspondence with referring physicians, and telephone interviews. Imaging data were not available for review. Data collected included demographics, age at diagnosis, family history, and reasons for diagnosis. Additionally, clinical characteristics, arterial pathology (aneurysms, dissection, rupture), intestinal perforation, pulmonary complications, management, and outcomes.

COL3A1 diagnostic testing was performed by Clinical Laboratory Improvement Amendments certified laboratories at the University Texas Health Science Center at Houston McGovern Medical School and Johns Hopkins Hospital, or at the National Institute on Aging. At the National Institute on Aging, the coding regions and flanking sequences of the *COL3A1* were amplified and sequenced. Primers were designed by Primer3 (http://frodo.wi.mit.edu/primer3/). Mutations were identified by alignment with the reference sequence (ENSG00000168542).

Data were analyzed using Microsoft Excel 2010 (Microsoft, Redmond, WA), SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL). Continuous variables are presented as mean, standard deviation, and ranges. Categorical variable are described by number and percentage. Continuous data were compared via independent samples *t* test with equal variances assumed and categorical data were compared using the Pearson chi square test. *p* values <0.05 were considered significant.

3 | RESULTS

Ninety-six genetically confirmed vEDS cases (38.5% males) were reviewed. The mean age at vEDS diagnosis was 30.4 ± 15.1 years (range 0.3–76 years). Table 1 summarizes the demographics and clinical characteristics of the cohort including the major and minor diagnostic categories. The most common reason for diagnosis was the presence of a family history of vEDS (47.9%) and presentation with an arterial pathology (32.3%) as detailed in Table 2.

A P/HTX occurred in 17 cases (35.3% male) at a mean age of 29.8 ± 10 years (range 17–44). There were no sex differences when compared to those who did not have a P/HTX (35.3% vs. 39.2%, $p = 0.762$) nor were there differences in the prevalence of family history (52.9% vs. 72.2%, $p = 0.121$). In 12 cases, the P/HTX preceded the first intestinal perforation event ($n = 5$) or the first arterial event ($n = 7$). In the remainder of the cases, three occurred during hospitalization for a life threating bleeding, while in two cases, the P/HTX was the only manifestation of the syndrome. What was notable is that the first P/HTX preceded diagnosis of the syndrome in the majority of cases ($n = 14$, 82.3%) with a mean age of P/HTX of 28.3 ± 9.5 years. In comparison, the mean age of the first intestinal and/or arterial complications of vEDS was 33.4 ± 9.7 years ($p = 0.012$). Many experienced recurrent P/HTX episodes ($n = 8$, 47%).

TABLE 1 Demographics, major and minor diagnostic criteria characteristics in 96 patients with confirmatory testing for vascular Ehlers–Danlos Syndrome (VEDS)

Variable (%, range)	*N* = 96
Male	37 (38.5)
Caucasian	87 (90.6)
Hypertension	15 (15.6)
Smoker (past or present)	10 (10.4)
Major diagnostic criteria	
Arterial pathology (aneurysms/dissection/rupture)	61 (63.5)
Intestinal perforation	15 (15.6)
Uterine rupture	1 (1.7)
Family history of vEDS	43 (44.7)
Minor diagnostic criteria	
Spontaneous pneumothorax/hemothorax	17 (17.7)
Thin translucent skin	54 (56.3)
Characteristic facial appearance	62 (64.6)
Carotid-cavernous sinus fistula	4 (4.2)
Hypermobility of small joints	45 (46.9)
Tendon/muscle rupture	7 (7.3)
Early-onset varicose veins	11 (11.4)
Easy bruising	70 (72.9)
Talipes equinovarus (clubfoot)	9 (9.4)

Management of P/HTX was variable ranging from noninterventional to pleural drainage to surgical. Table 3 provides the detailed information for the patients with P/HTX including the age at the first P/HTX, underlying mutation, details, and reason for vEDS diagnosis. Detailed treatment records were not available beyond this information.

3.1 | Comparison to the vEDS patients without pulmonary complications

When compared to the group of vEDS patients who did not have a P/HTX, arterial complications prevalence was similar (76.5% vs. 60.8%, $p = 0.222$) and the mean age of first arterial complications did not differ (34.2 ± 8 vs. 34.9 ± 10.8 years, $p = 0.818$).

Interestingly, the prevalence of the intestinal perforation was lower (35.3% vs. 11.4%, $p = 0.014$) and these patients were older when they had an intestinal perforation (34.2 ± 10.9 vs. 22 ± 8.9 years, $p = 0.031$).

TABLE 2 Primary reason for diagnosis and age of diagnosis of vascular Ehlers–Danlos Syndrome (VEDS)

	N = 96 (%)	Mean age at diagnosis (range)
Family history of vEDS	46 (47.9)	29.6 (0.3–76)
Arterial pathology	31 (32.3)	35.7 (17–58)
Intestinal perforation	7 (7.3)	32 (7–50)
Pneumothorax/hemothorax	2 (2.1)	37.5 (23–32)
Easy bruising	5 (5.2)	13.6 (4–39)
Characteristic facial appearance	1	31
Abnormal scarring	2 (2.1)	12.5 (12–13)
Other (ruptured spleen)	1	42
Unknown	1	37

TABLE 3 Age at the first pneumothorax and/or hemothorax, and management in patients with pathogenic COL3A1 variants confirming the diagnosis of vascular Ehlers–Danlos syndrome

Age/ sex	DNA/protein change/type	Age of arterial /intestinal pathology	Details and management	Reason for diagnosis
40M	c.997-2 A>G, p.(–) Splice site	43	First PTX prior to diagnosis. Had three episodes total, all managed successfully with chest tube and pleurodesis	Family history (daughter)
27M	c.2445+5G>A, p (–) Splice site	26	Pleural effusions during hospitalization for rupture splenic artery → thoracentesis → hemoptysis.	Postmortem diagnosis
25F	c.665G>T, p.(Gly222Val) Missense	50	PTX at age 25 "treated surgically", HTX at age 58 (no further details)	Colon rupture/family history (mother)
32F	c.1347+1G>C, p (–) Splice site	32	PTX during hospitalization for colon rupture	Colon perforation
35M	c.1744G>A, p.(Gly582Ser) Missense	38	PTX (no details on management)	Renal artery dissection
22F	c.1763_1769delGTGCTCCinsTAAG, p. (Gly588_Pro590delinsValSer) In-frame deletion/insertion	32	Recurrent PTX in same year, treatment with pleurodesis	Colon perforation
17F	c.2123G>A, p.(Gly708Asp) Missense	29	Recurrent right PTX x 3, later had left (no details on management)	Tibial artery aneurysm
44F	c.2284G>C, p.(Gly762Arg) Missense		HTX, supportive care only (diagnosis known at the time)	Family history (father)
38F	c.2284G>C, p.(Gly762Arg) Missense	43	HTX, supportive care only (diagnosis known at the time)	Family history (father)
31M	c.2456G>A, p.(Gly819Asp) Missense	31	PTX, then hemoptysis, cavitary lung lesions, thoracoscopy with biopsy	PTX/hemoptysis
18F	c.2816G>A, p.(Gly939Asp) Missense	18	PTX, chest tube placement → cystic lesion, pneumonia → thoracentesis → large hematoma formed.	Colon perforation
23F	c.3201+2T>C, p (–) Splice site	29	Unknown management	PTX
23F	c.3301G>A, p.(Gly934Arg) Missense	31	Right PTX treated with "surgery", left PTX small PTX treated conservatively	Family history (Brother)
21F	c.3499G>C, p.(Gly1000Arg) Missense	28	PTX treated with pleurodesis	Family history
17F	c.3093+2T>G, p(–) Splice site	17	Bilateral HTX found on autopsy. She presented with hemoperitoneum due to a ruptured right renal artery.	Postmortem diagnosis
"teens" M	c.955_974delGCTCGGGGTAATGACGGTGCinsTTTACATCGAGGGTTTTAAAGTTTACA, p.Ala319Phefs*13 Frameshift	41	Recurrent PTX x 3, all during teen years (specific age unknown, no other details)	Descending thoracic aortic dissection
43M	c.2870G>T, p.(Gly957Asp) Missense	42	Spontaneous right HTX, subsequent recurrent PTX during admission post incisional hernia repair	Splenic artery rupture

PTX = pneumothorax; HTX = pneumohemothorax.

The mean age of death was not different between the two groups at 29.0 ± 10.7 years (range 17–43 years) in the group with P/HTX compared to 38.5 ± 17.8 (range 25–79 years) in the group without P/HTX. None of the deaths was related to the P/HTX.

4 | DISCUSSION

This report adds an important insight into the natural history of vEDS. The vascular subtype of EDS is the only subtype that has pulmonary complications (spontaneous pneumothorax or hemothorax) as one of the diagnostic criteria (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998; Malfait et al., 2017). Our report demonstrates that P/HTX, which occurred in 17.7% of this cohort, appears to occur as an early manifestation of vEDS preceding the intestinal and arterial complications thus offers an opportunity for early diagnosis of the syndrome. Establishing the diagnosis in vEDS is a challenge even for experienced clinicians due to the rare nature of the disease and the heterogeneous clinical presentation (Byers et al., 2017; Eagleton, 2016; Shalhub et al., 2014). In 50% of cases, the mutation is a de-novo mutation, thus a family history is lacking. Moreover, while some vEDS patients do demonstrate a classic phenotype of easy bruising, translucent skin, and a distinctive facial appearance (prominent eyes, a thin pinched nose, small lips, hollow cheeks, and lobeless ears) (Beighton et al., 1998), these findings are not seen in all individuals with vEDS (Shalhub et al., 2014). For this reason, the diagnosis may not be suspected until severe complications occur. In the largest series of vEDS, only 30% of the patients were diagnosed prior to developing a serious

TABLE 4 Case reports of spontaneous pneumothorax or pneumohemothorax in patients with confirmatory testing for vascular Ehlers–Danlos syndrome

Manuscript	Age, sex	Diagnosis	Family history	History/outcomes
Abrahamsen et al.	19M	c.2896G>T, p.Gly966Cys	N/A	Intermittent cough, blood-tinged sputum for two months preceding massive hemoptysis. PTX treated with chest tube. Recurrence for three times. Resection of sub pleural bullae and mechanical pleurodesis x 2, subsequent left PTX. No arterial or colon pathology
Kashizaki et al.	64F	c.2411G>T p.Gly804Val	No	Right HTX, treated with chest tube then thoracoscopy/fibrin glue. Preceded HTX: Age 49, intractable uterine hemorrhage, age 62 cutaneous arteriovenous fistulae. Post diagnosis: Aneurysms in 64 celiac, splenic artery, superior mesenteric artery, bilateral renal and iliac arteries
Kang et al.	18M	c.899G>A, p. Gly300Asp	No	Hemoptysis → lung mass on imaging → thoracoscopy, complications prompted lobectomy and subsequent reoperation
Ahmad Dar et al.	18M	p. Gly603Asp	No	PTX initially, then HTX three years later. 3 years later, treated with resection and wedge biopsy
Omori et al.	20M	IVS 24G+1 to A	N/A	Recurrent PTX history prior to his colon perforation. No arterial pathology. Diagnosed after colon perforation
Selim et al.	11M	p. Gly727Ala	Yes	Recurrent hemoptysis and pneumothorax. Lung pathology: Fibrous nodules with osseous metaplasia, diffuse alveolar hemorrhage. Left pleural effusion and small PTX at age 21, thoracentesis left pleural effusion and small PTX at age 21, thoracentesis. No arterial or colon
Sadakata et al.	23M	c.2528G>A, p.Gly843Glu	N/A	6 episodes of pneumothorax and alveolar hemorrhage, treatment with thoracentesis. No arterial or colon pathology
Ishiguro et al.	17M	c.1925G>A, P.Gly603Asp	No	Thick-walled cavity in the left lower lobe, thoracoscopy. Subsequently, hemoptysis and bloody sputum once a year. Diagnosed after wedge biopsy. Arterial abnormality 7 years post PTX: Right ulnar, celiac, and left iliac artery aneurysms

PTX = pneumothorax; HTX = pneumohemothorax.

complication (Pepin, Schwarze, Superti-Furga, & Byers, 2000). Indeed in our cohort, the initial P/HTX event preceded the arterial pathology and intestinal perforation in 70% of the cases.

Prompt accurate diagnosis of vEDS is imperative given the serious implications in term of management recommendations for the patient and family members (Byers et al., 2017; Pepin et al., 2014; Shalhub et al., 2014). The diagnosis can be confirmed by obtaining a skin biopsy or by genetic testing for pathogenic variants in the *COL3A1*, the latter is the contemporary approach to diagnosis (Byers et al., 2017; Malfait et al., 2017). Using the genetic testing to establish the diagnosis of vEDS is an imperative given that spontaneous PTX also occur in association with other syndromes such as Birt-Hogg-Dube (22%) syndrome, Marfan syndrome (14%), and less commonly in association with Loeys-Dietz syndrome and homocystinuria (Bass et al., 1997; Bock, Lohse, Madsen, & Hilberg, 2018; Corsico et al., 2014; Meester et al., 2017).

The body of literature regarding pulmonary complications in vEDS consists of case reports (Abrahamsen, Kulseth, & Paus, 2015; Dar, Wani, Mushtaque, & Kasana, 2012; Gu et al., 2018; Ishiguro et al., 2009; Kashizaki, Hatamochi, Kamiya, Yoshizu, & Okamoto, 2013; Omori et al., 2011; Sadakata et al., 2010; Selim, Lane, Rubinowitz, & Siner, 2010). The majority of these case reports include males with an average age of 24 years (range 11–64) at presentation, not unlike the mean age of initial P/HTX presentation in our cohort. In a classic series of vEDS arterial complications from the Mayo clinic, the prevalence of P/HTX was noted to be 16%; similar to our data here; though clinical detail regarding the P/HTX in that cohort was not the focus of the manuscript (Oderich et al., 2005).

Due to the rarity of vEDS and lack of large case series, our understanding of P/HTX in this population is limited. The association between spontaneous P/HTX and the absence of type III collagen in patients with vEDS was initially suggested in 1980 (Clark, Kuhn 3rd, & Uitto, 1980). It has been proposed that pleural lesions leading to P/HTX are caused by weakening of the pleura and arterial fragility since large areas of ecchymosis in the thoracic cavity are frequently noted (Dowton et al., 1996; Kawabata et al., 2010; Sadakata et al., 2010). Lung pathology from vEDS patients reveals intra-alveolar and intra-pulmonary hemorrhage (Purohit et al., 2009). Other pulmonary manifestations include thick-walled cavities as a result of previous lung hemorrhage, bullous lung disease, pan acinar emphysema, pulmonary cysts, and bronchiectasis (Selim et al., 2010). In rare cases massive pulmonary hemorrhage leads to acute respiratory insufficiency (Hatake et al., 2013). In a study of nine patients with vEDS who underwent lung biopsy, lobectomy or autopsy, most pulmonary lesions were idiopathic lung tissue lacerations (Kawabata et al., 2010). We summarize contemporary case reports of spontaneous P/HTX in patients with confirmatory testing for vEDS in Table 4.

Management recommendations specific to P/HTX in patients with vEDS are lacking. In our series and in other case reports, pleural drainage via chest tube is used when required. What is clear is that vEDS patients with P/HTX have a high rate of recurrences, which are then treated with video-assisted thoracoscopic surgery, pleurodesis, and application of fibrin glue. Open surgical interventions have been described in cases that could not be otherwise managed including lobectomy for life-threatening hemorrhage (Kawabata et al., 2010).

The study is limited by its retrospective nature and that the original study design was focused on the arterial complications of vEDS

rather than the pulmonary complications. The data were obtained via medical records abstraction, in addition to patient questionnaires with most of the P/HTX events occurring prior to the syndrome diagnosis as such the information regarding the P/HTX events was limited to a mention in the past medical history rather than having full records available to review. This study was not designed to assess how predictive P/HTX is of vEDS diagnosis.

In summary, spontaneous P/HTX in vEDS occurs at an earlier age than the arterial or colonic manifestation of the syndrome. Thus vEDS should be considered in the differential diagnosis of the causes of a spontaneous P/HTX and evaluation for other features consistent with vEDS should be performed. If these features are present in addition to the spontaneous P/HTX then diagnostic studies to determine if the individual has vEDS are recommended.

5 | CONCLUSIONS

Spontaneous pneumothorax or hemothorax is an early manifestation of vEDS frequently preceding an arterial complication or intestinal perforation. Thus, a spontaneous P/HTX in a young patient should trigger a differential diagnosis that includes vascular Ehlers–Danlos syndrome. This should lead to an investigation of other vEDS features and subsequent genetic testing if vEDS features are present.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest or financial disclosures.

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