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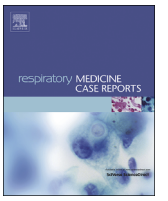

Case Report

Pulmonary *Mycobacterium avium* complex infection with vascular Ehlers–Danlos syndrome: A case report

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ABSTRACT

A female patient developed multiple intestinal perforations at 31 and 43 years of age. Because of her family history of pneumothorax and intestinal perforation, Ehlers–Danlos syndrome (EDS) was suspected when she visited our hospital at 52 years. She was diagnosed with vascular Ehlers–Danlos syndrome (vEDS) and developed bilateral external iliac artery dissection. A CT scan at the time of admission revealed granular and infiltrative shadows in both lungs with bronchiectasis. The patient was also diagnosed with *Mycobacterium avium* complex (MAC) pulmonary disease, and drug susceptibility to clarithromycin was confirmed. After treatments with rifampicin, ethambutol, and clarithromycin were started, the acid-fast bacilli cultures taken from sputum were negative, and respiratory symptoms partially improved after about 1 month. vEDS is reportedly associated with lung diseases, such as pneumothorax and cystic lung lesions, but there are few reports of respiratory infections with vEDS. Moreover, there are no reports of complications associated with MAC disease. We report a case of vEDS with rare complications and suggest the possible mechanism of infection.

1. Introduction

Ehlers–Danlos syndrome (EDS) is a genetic disease characterized by hyperextensibility of the skin and joints and fragility of various tissues. Currently, it is classified into 13 subtypes [1], and clinical criteria are provided for each classification. Vascular Ehlers–Danlos syndrome (vEDS) is rare and is known as the most severe subtype. The main pathological finding of vEDS is a decrease in collagen III due to the *COL3A1* gene mutation. The weakness of the blood vessels and intestinal tracts causes vascular rupture and intestinal perforation. Cystic pulmonary lesions in hematogenous sputum may occur frequently due to a decrease in lung elastic fibers [2]. Complications of respiratory diseases, such as bronchiectasis and pneumothorax, have also been reported [4–6].

A female patient who was diagnosed with vEDS developed bilateral iliac artery dissection, and a chest CT image taken at that time incidentally revealed a left pneumothorax and granular and infiltrative shadows in both lungs. *M. avium* was detected in two separate cultures from sputum samples, and she was diagnosed with pulmonary MAC disease. Pulmonary MAC disease has been reported to be

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associated with some chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and bronchiectasis. However, despite reports of MAC disease with vEDS being rare, we report on the course of this rare condition in this case.

2. Case report

A 52-year-old woman underwent surgical treatment at another hospital for intestinal perforation. EDS was suspected due to the fragility of the intestinal tissues during surgery and a family history of pneumothorax and intestinal perforation. The patient consulted the genetics department of our hospital, where genetic testing detected a *COL3A1* gene mutation. Based on the patient's past medical history and family history suggestive of EDS, the diagnosis of vEDS was confirmed, and the patient has since visited the outpatient clinic regularly. She visited our hospital for chief complaints of sudden abdominal pain at the periumbilical region and back pain, and was admitted to the hospital with bilateral external iliac artery dissection detected on CT scans. At the same time, chest X-rays revealed granular and infiltrative shadows in both lungs with bronchiectasis and a left pneumothorax, and she subsequently consulted our respiratory department.

In her medical history, she developed idiopathic small bowel perforation and peritonitis at 32 years, and at 44 years she underwent surgical treatment for perforation of the descending colon, receiving a colostomy. She also had a history of hypertension and reflux esophagitis and had undergone balloon dilatation for esophageal stricture. In her family history, her son had a history of pneumothorax and intestinal perforation, and her daughter also had a history of pneumothorax. Analysis of the gene revealed *COL3A1*:c.2337G > A which showed single base skipping in the last nucleotide of exon 33, and she was diagnosed with vEDS using genetic testing. She had a history of smoking two cigarettes daily for 6 years but no history of drinking alcohol. Findings on admission: height 153 cm, weight 29 kg, body mass index (BMI) 12.4, body temperature 36.1 ˚C, blood pressure 117/71 mmHg, pulse rate 66 bpm, and arterial oxygen saturation of pulse oximetry 97 %. No abnormal breath sounds were heard, tenderness was observed below the umbilicus, and there were signs of skin hyperextension in the upper limbs. Laboratory findings are shown in Table 1. Chest X-ray examination on admission showed granular shadows in both the right and left upper lobes and infiltration in the left lower lung field. Chest CT on admission showed consolidation in the left lower lobe, granular and nodule shadows in both the right and left lobes, bronchiectasis, and left pneumothorax (Fig. 1).

Regarding the bilateral external iliac artery dissection, which was the reason for the patient's hospitalization, the patient was admitted to the intensive care unit. Her blood pressure was controlled, and bilateral external iliac artery dissection and left pneumothorax spontaneously resolved with only conservative treatment. Based on CT findings, a chronic respiratory infection, including possible mycobacterial infection, was suspected, and sputum tests were conducted. Bacteriological tests showed only the growth of resident bacteria, but acid-fast bacterial tests over three days revealed that the sample on the first day indicated tuberculosis and was MAC PCR negative. The smear from the second day showed a few bacteria, and cultures from the second and third days grew *Mycobacterium avium* (*M. avium*). The minimum inhibitory concentrations (MICs) for *M. avium* were: streptomycin 16 μg/mL, ethambutol (EB) 8 μg/mL, kanamycin 16 μg/mL, rifampicin (RFP) 0.125 μg/mL, levofloxacin 0.03 μg/mL, rifabutin 4 μg/mL, clarithromycin (CAM) 1 μg/mL, ethionamide 16 μg/mL, and amikacin 16 μg/mL. The final diagnosis was CAM-sensitive pulmonary MAC infection with no drug resistance. There were no cavitary changes in the pneumonia, and she was diagnosed with the nodular-bronchiectasis type. On day 55, she started treatment with three drugs: RFP 300 mg/day, EB 500 mg/day, and CAM 400 mg/day. On day 92, both the smear and culture results of a sputum mycobacterial test were negative and remained negative. A CT scan also showed improve-

Table 1
Laboratory findings on admission (summary of investigations carried out on the patient).

Test	Result	Reference range
White blood count	8100	3300–8600/μL
Neutrophil count	82.8	40–70 %
Lymphocyte count	13.7	27–47 %
Hemoglobin count	13.6	11.6–14.8 g/dL
Platelet count	229,000	158,000–348,000/μL
Serum total protein	7.6	6.6–8.1 g/dL
Albumin	4.2	4.1–5.1 g/dL
Creatinine	0.51	0.46–0.79 mg/dL
Blood urea nitrogen	10.3	8.0–20.0 mg/dL
Aspartate transaminase	22	13–30 U/L
Alanine transaminase	10	7–23 U/L
Sodium	142	138–145 mmoL/L
Potassium	3.8	3.6–4.8 mmoL/L
C-reactive protein	0.14	≤0.14 mg/dL
N-terminal pro-brain natriuretic peptide	90.7	≤124 pg/mL
Hemoglobin A1c	5.8	≤6.0 %
PT	12.3	10.0–14.0 seconds
APTT	41.9	24.0–39.0 seconds
D-dimer	0.6	≤0.5 μg/mL
T-spot® TB	Negative	Negative
Anti-GPL-core IgA negative	>10	<0.7 U/mL

Abbreviations: PT; prothrombin time, APTT; activated partial thromboplastin time.

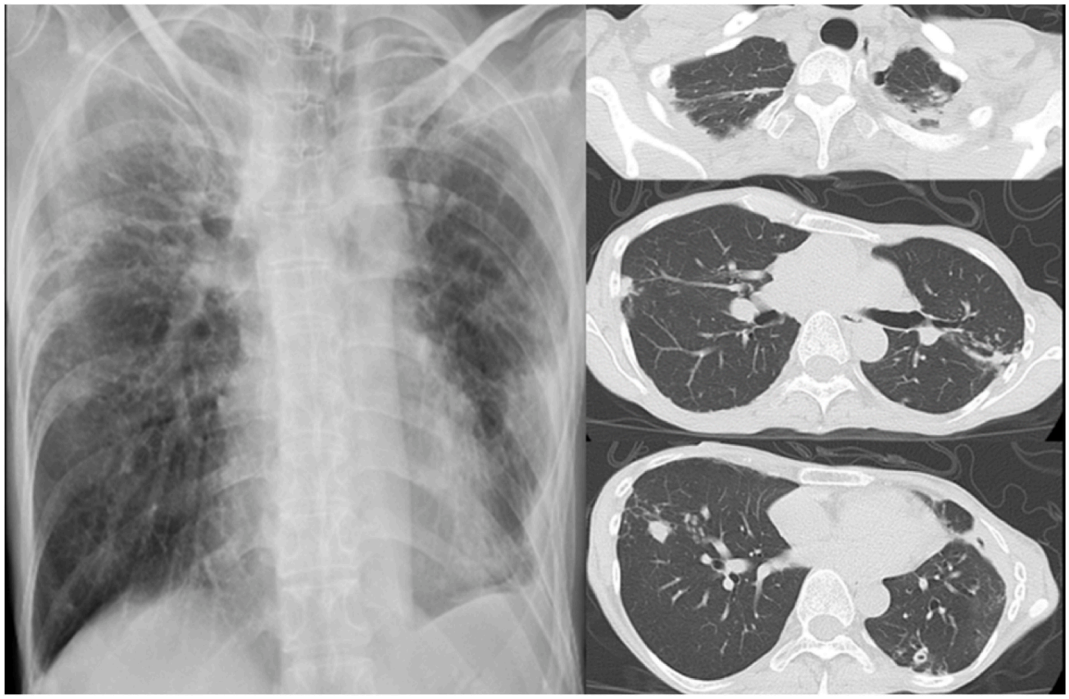

Fig. 1. Chest X-ray examination on admission showed granular shadows in both the right and left upper lobes and infiltration in the left lower lung field. Chest computed tomography on admission showed consolidation in the left lower lobe, as well as granular and nodule shadows in both the right and left lobes, bronchiectasis, and left pneumothorax.

ment in infiltration shadows in the bilateral lower regions. Since gastrointestinal symptoms did not appear, the dose of CAM was increased to 600 mg/day on day 272, and the treatments were completed on day 804. After the treatments, the pulmonary MAC disease remained stable, and the sputum mycobacterial test remained negative. As for the course of the treatment for vascular EDS, she developed a right spontaneous pneumothorax on day 92 and a right intercostal artery rupture on day 406, both of which improved with rest and conservative management (Figs. 2 and 3).

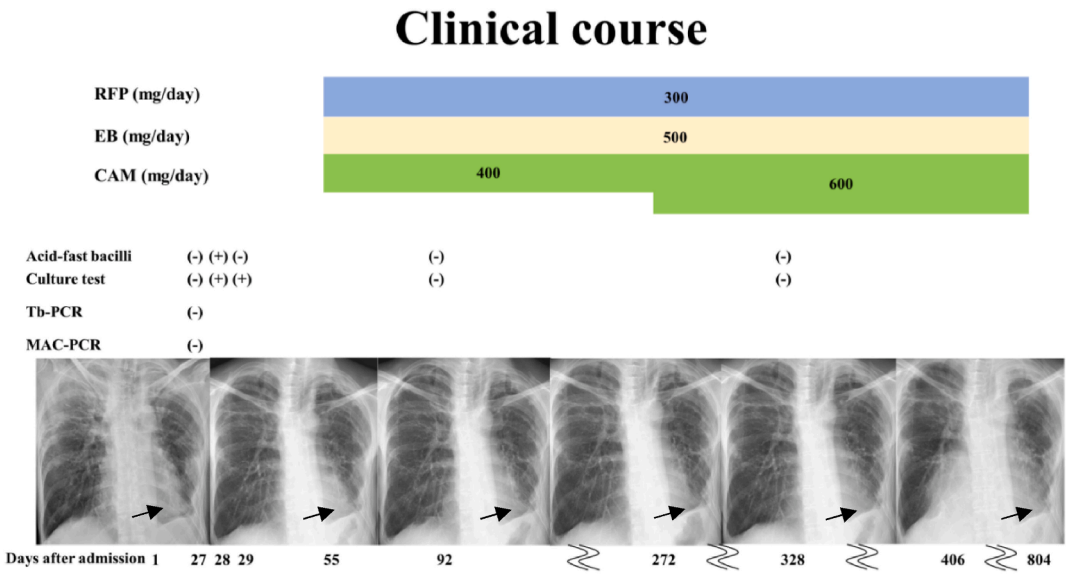

Fig. 2. The treatment with RFP, EB, and CAM continued for over 1 year after the culture was negative from day 55 to day 804. She developed right pneumothorax on day 92 and right hemopneumothorax on day 406. Both improved with rest and conservative management. Granular shadows in both the right and left upper lobes and infiltration in the left lower lung field (black arrows) also improved.

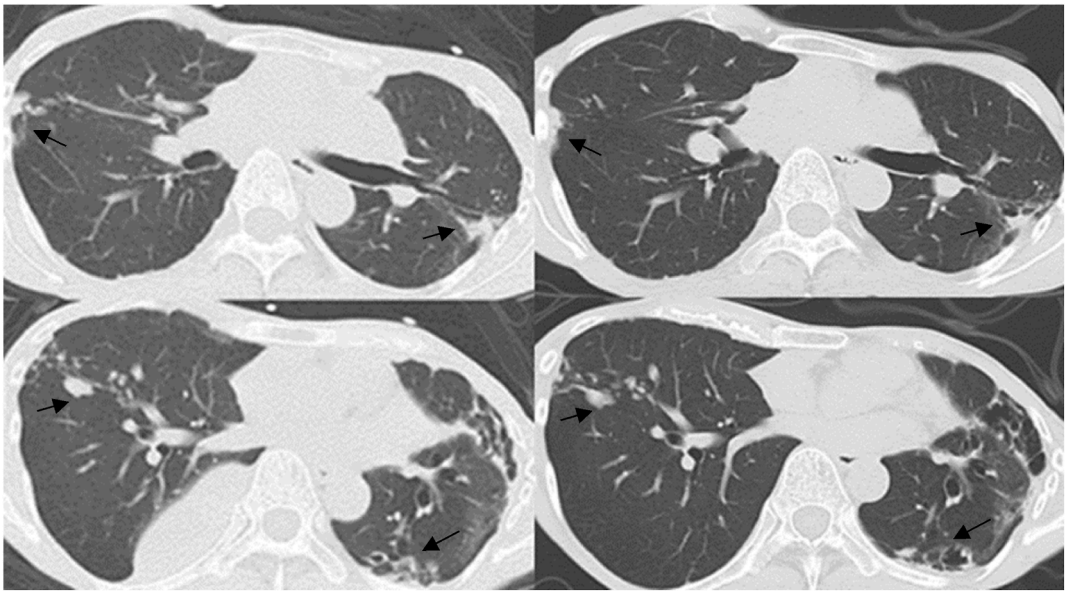

Fig. 3. CT images of the left side showed right hemopneumothorax on day 406. Images of the right side were taken at the end of MAC treatments. Both show improvements of granular shadows and consolidations (black arrows) in the bilateral lungs.

3. Discussion

EDS is an autosomal dominant genetic disease based on the weakness of connective tissue throughout the body, including the skin, joints, and blood vessels. EDS is classified into 13 subtypes [1]: each has mutations in genes or enzymes that produce a specific collagen. Because of the rarity of EDS, its exact incidence and prevalence are unknown, and there are no effective treatments for this disease. Among these subtypes, vEDS is often reported as being the most severe. Its frequency in past cohort studies was estimated at 1/50,000–1/250,000 people, and the median survival age as young as 48 years [3]. The diagnostic criteria for vEDS include standard symptoms (thin and semi-skinned skin) and the presence of two or more of transparent and ruptured arteries/intestines/uterus, easy bruising, and characteristic facial symptoms (large eyes, small chin, sunken cheeks, thin nose and lips, and lobeless ears). Abnormality in type III procollagen production in cultured skin fibroblasts or *COL3A1* gene mutations is also observed. The main pathology is a decrease in collagen III, which forms connective tissue, thus causing fragility of blood vessels and the intestinal tract. Since collagen III also plays an important role as extracellular matrix (ECM) in the lungs, complications of pneumothorax, hemothorax, hemoptysis, and hemocystic lung lesions have been reported when collagen is deficient [4–8]. Many cases of vEDS with pulmonary complications have been reported (see Table 2); however, there have been no reports of complications, such as chronic respiratory tract infections. In this case, the patient's condition was complicated by a nontuberculous *Mycobacteria* infection.

More than 200 species and subspecies of nontuberculous *Mycobacteria* have been reported, and they are widely present in the natural environment, including soil and water sources. *M. avium* is a bacterial species that can infect humans and has been frequently reported. Bathrooms are reportedly a source of infection, and the incidence rate is higher in those who are frequently exposed to soil, such as farmers and gardeners [45,46]. Although environmental factors are involved, comorbid chronic respiratory diseases such as COPD and bronchiectasis in the host are also reportedly a factor [47]. Despite being a common bacterium that patients can be exposed to on a daily basis, the symptoms are limited or lacking in some, so the genetic etiology may be responsible. In recent years, genetic abnormalities in the *CHP2* region have been shown to be involved in the onset of the disease [48]. However, the mechanism of infection remains unclear. As far as we have investigated, only one case of fungal endocarditis has been reported as a combination of vEDS and infection [49]. Although there are no reports of comorbidity with vEDS and pulmonary MAC disease, the following points are assumed to be grounds for considering it as a risk factor for the development of MAC disease.

First, it has been demonstrated that *M. avium* binds to damaged non-ciliated epithelium in patient tissues. MAC also possibly adheres to the ECM in areas of epithelial injury via fibroblast activation proteins and to mucus with a fibrous appearance via another adhesin. Chronic epithelial damage reportedly exposes the ECM and reduces mucus clearance, which is thought to increase the likelihood of respiratory tract infection in MAC [50]. It is widely known that ECM plays the role of a scaffold for cell and matrix adhesion, for example, in fibronectin and collagen. The main pathology of vascular EDS is the abnormal production of collagen III, which is thought to lead to decreased ECM function and cause MAC infection.

The second point is the low nutritional status of the patient, which can lead to the development of chronic lower respiratory tract infections. The above-mentioned cohort study reported that intestinal perforation itself has no correlation with mortality rate, but vascular damage is correlated with mortality rate and survival cases in patients with a history of surgery for intestinal perforation. As a result, it is thought that when patients are in such a state, such as after a stoma has been created, they are likely to be at a higher risk of decreased intestinal function and malnutrition compared to healthy individuals. It is thought that our patient's very low BMI and associated malnutrition created an environment conducive to MAC infection, which put her at risk for developing the disease.

Table 2
Case reports of vEDS with pulmonary complications. (To provide a comprehensive review of the vEDS with pulmonary complications, we carried out a PubMed search to identify all papers published in English during the period 1994–2023.)

Author	Age	Sex	Pulmonary complications
Junping S et al. [4]	22	Male	Pneumothorax, hemoptysis, and intrapulmonary cavitary lesions
Taurino J et al. [9]	26	Male	Pneumothorax and pulmonary bleeding
Chhabria MS et al. [10]	60	Female	Chronic obstructive pulmonary disease
Guo T et al. [11]	14	Unknown	Pneumothorax and migratory lung nodules
Wang P et al. [5]	17	Male	Intrapulmonary hemorrhage
Pereira C et al. [12]	38	Female	Bilateral pulmonary thromboembolism
Mangiameli G et al. [13]	50	Female	Extra-pleural hematoma
Tanaka S et al. [7]	29	Male	Hemothorax and a pulmonary nodular lesion
Kim MJ et al. [14]	19	Male	Pneumothorax, hemoptysis, multiple pulmonary cystic lesions, and several nodules
Yoshizumi Y et al. [15]	30	Male	Lung laceration, vascular disruption, hemosiderosis, emphysema, and diffuse pulmonary ossification
Mendonça Almeida L et al. [16]	19	Male	Hemorrhagic parenchymal cavitation and pulmonary embolism
Michell H et al. [17]	41	Female	Hemopneumothorax
Wan T et al. [18]	24	Male	Pneumothorax and intrapulmonary cavitary lesions
Sakai K et al. [19]	52	Male	Hemothorax
Park MA et al. [20]	18	Male	Pneumothorax, pulmonary capillary hemangiomatosis, and pulmonary cystic lesions
Berezowska S et al. [21]	18	Female	Hemoptysis, pneumothorax, emphysema, and fibrous nodules containing ossifications
Álvarez K et al. [22]	50	Male	Hemothorax
Nakagawa H et al. [23]	17	Male	Bilateral pneumothorax
Ruggeri P et al. [24]	37	Male	Hemoptysis and pulmonary emphysema
Abrahamsen BJ et al. [25]	19	Male	Bilateral pneumothorax, hemoptysis, and intrapulmonary cavitary lesions
Kadota et al. [26]	24	Male	Hemoptysis and pneumothorax
García Sáez D et al. [27]	29	Female	Chronic obstructive pulmonary disease
Verbert A et al. [28]	15	Male	Pneumothorax
Kashizaki F et al. [29]	64	Female	Hemothorax
Sa YJ et al. [30]	8	Male	Congenital cystic adenomatoid malformation of lung
Hatake K et al. [31]	unknown	Male	Pulmonary hemorrhage and fibrous nodules containing benign metaplastic bone in lung
Sadakata R et al. [32]	23	Male	Hemopneumothorax
Escribano N et al. [33]	23	Male	Hemoptysis, hemopneumothorax, and acute diffuse alveolar hemorrhage
Iida Y et al. [34]	20	Male	Hemothorax
Ishiguro T et al. [35]	17	Male	Pneumothorax, cavity, organizing hematoma, and a fibrous nodule in lung
Purohit N et al. [36]	22	Female	Hemoptysis, hemopneumothorax and a cystic lesion
Watanabe A et al. [37]	16	Female	Hemoptysis and cavitary formation of the lung
Maltz SB et al. [38]	28	Male	Pulmonary contusion and pneumothorax
Aru GM et al. [39]	8	Male	Hemothorax
Iglesias JL et al. [40]	8	Female	Diaphragmatic hernia
Yost BA et al. [41]	27	Male	Acute diffuse alveolar hemorrhage
Murray RA et al. [42]	Unknown	Unknown	Parenchymal cysts and fibrous nodules
Whinney D et al. [43]	28	Male	Pneumothorax
Herman TE et al. [44]	18	Male	Hemorrhagic cavities

The third point is the global increase in incidence rates for pulmonary nontuberculous mycobacterial disease (PNTMD) [51].Especially, incidence rates of PNTMD in Japan are the highest in the world. The reasons for the increase in incidence rates may be the simplified diagnosis, increased awareness by medical staff, population aging, and increased frequency of medical checkups with CT [52].

Many cases of vEDS with cystic lesions and several nodules have been reported. It is difficult to differentiate between vEDS and PNTMD in CT findings. Furthermore, the acute onset of severe conditions in vEDS patients may prevent diagnosis of PNTMD from sputum examination.

Additionally, as mentioned above, genetic abnormalities that are correlated with MAC disease in the host have been discovered, but the genes associated with the currently known EDS patients and the host with MAC disease are different, and the chromosomes of each gene exist in separate regions. Currently there is no evidence for genetic involvement between MAC and EDS.

International guidelines for the treatment of nontuberculous mycobacterial (NTM) pulmonary disease have been revised frequently, and although treatment regimens have been established for relatively frequently occurring bacterial species, there are many cases in which the disease is difficult to treat. In cases of MAC disease, treatment based on macrolide and amikacin susceptibility is recommended, and in cases of macrolide susceptibility, combination therapy with three drugs, including macrolides (clarithromycin or azithromycin, rifampicin or rifabutin, and ethambutol), is recommended as standard therapy.

On the other hand, in cases of cavitation formation, severe bronchodilation, or macrolide resistance, concomitant use of amikacin or streptomycin is recommended, and in refractory cases, use of amikacin liposome inhalation suspension is also recommended. The treatment period should continue for 1 year after confirmation of negative bacterial excretion from sputum. In this case, the patient was diagnosed with macrolide-sensitive MAC disease due to the nodular-type shadow, so three-drug therapy of clarithromycin, rifampicin, and ethambutol was performed as standard therapy for about 2 years. As a result, sputum excretion decreased, and the imaging findings partially improved. After finishing treatment, sputum excretion remained decreased.

We treated a case of pulmonary MAC disease complicated by vEDS that suggested vEDS may be a risk factor for the development of NTM pulmonary disease. Currently, there is no curative treatment for vEDS, so the management of complications is important. In summary, if we see respiratory diseases in vEDS patients, we need to check for chronic respiratory infections.

Consent for publication

Informed consent was obtained for this experimentation.

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CRediT authorship contribution statement

Ken Okamura: Conceptualization, Writing – original draft, Writing – review & editing. **Rintaro Noro:** Conceptualization, Writing – original draft, Writing – review & editing. **Toru Tanaka:** Investigation. **Takeru Kashiwada:** Investigation. **Yosuke Tanaka:** Investigation. **Yoshinobu Saito:** Investigation. **Kazue Fujita:** Investigation. **Koichi Akutsu:** Investigation. **Tomoko Sahara:** Investigation. **Koichiro Kamio:** Writing – review & editing. **Takeshi Yamada:** Investigation. **Kazuo Kasahara:** Writing – review & editing. **Masahiro Seike:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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