Case Report

DOI: 10.7860/JCDR/2024/69837.19645

An Unusual Association of Interstitial Lung Disease with Pulmonary Arterio-venous Malformation: A Case Report

Internal Medicine Section

RAHUL MITTAL[1], PRAVEEN RAJ SEETHARAMAN[2], SUBRAMANIAN SURIYAN[3], NAGARJUN SAKTHIVEL[4]

ABSTRACT

Interstitial Lung Disease (ILD) in diffuse cutaneous Systemic Sclerosis (SSc) patients is present in about 53% of cases and 35% in cases with limited cutaneous SSc. Even though there are only a few case reports of ILD associated with Hereditary Haemorrhagic Telangiectasia (HHT), a direct association of SSc and HHT has not been reported. Hence, little is known about the pathogenetic link between the two diseases. In this case report, a 24 years old married female patient presented with progressive breathlessness for one year. Initial evaluation of the patient suggested the diagnosis of SSc based on clinical findings like sclerodactyly along with telangiectasia. High Resolution Computed Tomography (HRCT) of the chest revealed the presence of pulmonary arteriovenous malformation along with ILD. Past medical history and family history of epistaxis for three generations suggested the diagnosis of HHT. This case reports a rare association of Connective Tissue Disease (CTD) and an autosomal disorder of vascular dysplasia with overlapping features of telangiectasia. This case is presented to highlight the possible association of HHT with CTDs. With the currently available literature, an attempt is made to find a plausible pathogenetic link between HHT and SSc. Transforming Growth Factor-β (TGF-β) is a pleiotropic growth factor that regulates the growth and differentiation of various cell types, and immune regulation has been implicated in the pathogenesis of both HHT and SSc. The other pathogenetic mechanism common to both diseases is impaired nitric oxide-mediated vasodilation. This case report emphasises the need for further research for a better understanding of the pathogenesis of both diseases.

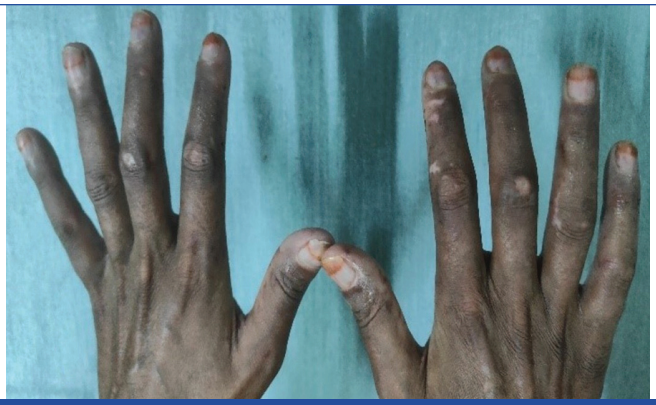
Keywords: Diffuse, Hereditary haemorrhagic, Scleroderma, Telangiectasia, Transforming growth factor beta

CASE REPORT

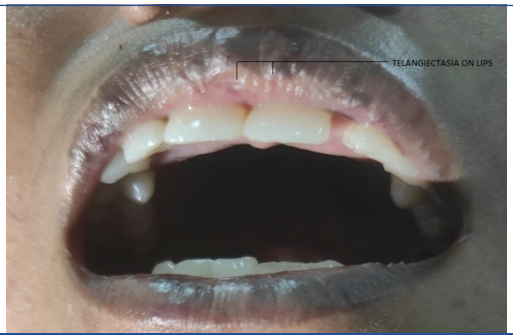
A 24-year-old married female who is a homemaker, presented with progressive breathlessness for a duration of one year that worsened with exertion. The patient also had a cough with white and mucoid expectoration for one year, associated with intermittent haemoptysis. Her history also revealed dry skin, pigmentary changes, tightening of the skin, generalised pruritus, and hair loss. She had complaints of joint pain in both elbow and knee joints, difficulty in rising from a sitting position, and limited movement in the small joints of all limbs. She also had difficulty in opening her mouth, dysphagia, a burning sensation in her mouth upon taking spicy foods for one year, along with intermittent nausea and vomiting. These symptoms started when the patient conceived one year back but continued to progress even though she had a spontaneous abortion at four months of gestation. No other significant respiratory or cardiac symptoms were present, and there was no history of drug intake, radiation exposure, or occupational or environmental exposure. The patient denied any similar significant illnesses in her family during the initial evaluation.

On examination, the patient was conscious, in mild respiratory distress, with 97% oxygen saturation on room air. Systemic examination of the respiratory system was found to be normal. A careful dermatological examination was done with assistance from a dermatologist reveaing the following signs.

- Diffuse tightening of the skin over the face, neck, and both upper and lower limbs-sclerodactyly [Table/Fig-1];
- Ragged cuticle over fingernails, with pitted scars over the tips of the digits;
- Salt-and-pepper pigmentation over the neck, upper and lower limbs, and lower abdomen;
- Ingram sign (inability to retract the lower eyelid);
- Barnett's neck sign (ridging and tightening of the neck on extension);
- Mizutani sign (disappearance of peaked contour on finger pads and replaced with hemisphere-like fingertip contour);
- Microstomia with a fish-mouth appearance [Table/Fig-2];

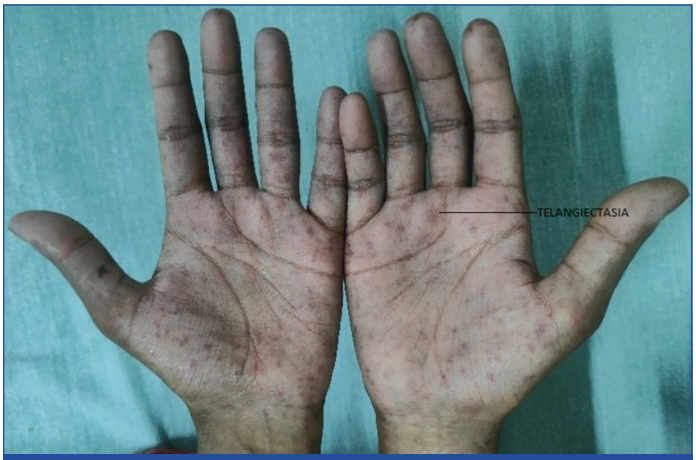


[Table/Fig-1]: Dermatoscopic image showing thickening of skin of hands with contractures (sclerodactyly).



[Table/Fig-2]: Dermatoscopic image showing telangiectasia over lip, fish mouth appearance.

- Fingers-calcinosis cutis and pan digital clubbing;
- Tiny erythematous macules over palmar surfaces [Table/Fig-3];



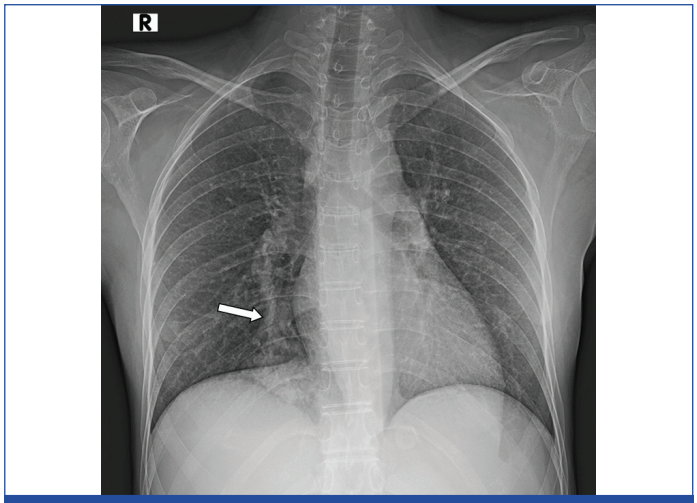
[Table/Fig-3]: Dermatoscopic image showing multiple erythematous macules over palms with telangiectasia.

Small red clusters of dilated vessels over the face, lips, palate, tongue, palms, and soles-telangiectasia [Table/Fig-2-4].

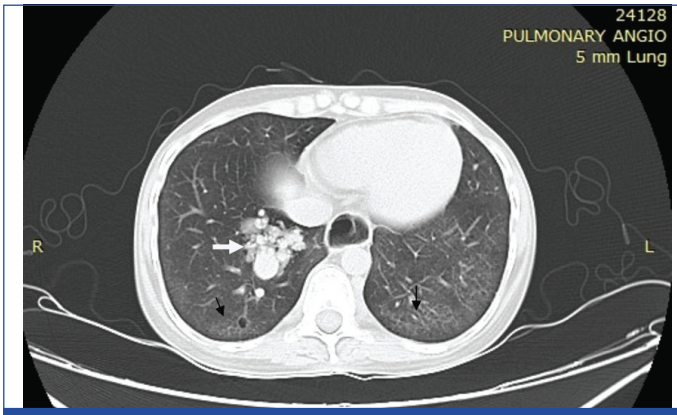
[Table/Fig-4]: Dermatoscopic image showing telangiectasia over face.

According to the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification [1], the patient had a score of 16 based on the clinical findings, which suggested a definitive diagnosis of SSc. Indirect immunofluorescence was positive for Antinuclear Antibody (ANA) (3+) with a nuclear-dense, fine-speckled fluorescence pattern. Anti-topoisomerase-1 antibody (Anti-Scl-70) was also positive, confirming the diagnosis of SSc. Chest radiography showed haziness in the right lower zone [Table/Fig-5].

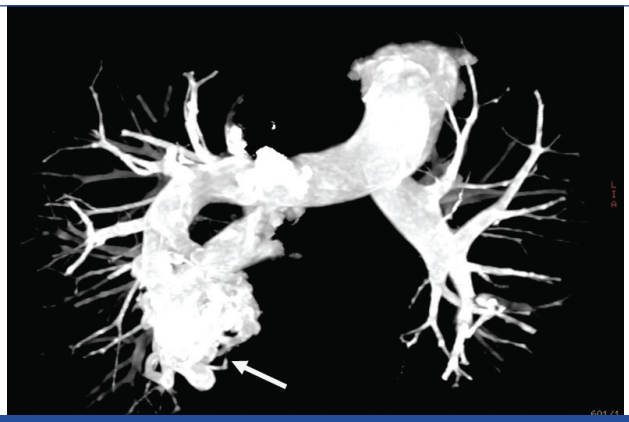
HRCT chest showed bilateral lower lobe subtle ground glass opacities with septal thickening in bilateral lung fields with subpleural sparing, suggestive of Non-Specific Interstitial Pneumonia (NSIP) pattern, a dilated oesophagus throughout its course. In addition to the above findings, HRCT also revealed multiple tangled dilated hyperdense structures in the medial segment of the right lower lobe, draining the right inferior pulmonary vein suggestive of AVM. Computed Tomographic Pulmonary Angiography (CTPA) revealed an NSIP pattern [Table/Fig-6], multiple tangles of vessels measuring 3.3×3.7×3.3 cm draining into the right inferior pulmonary vein [Table/Fig-7], which was dilated 11 mm with feeding from the coeliac artery [Table/Fig-8]. An arterio-venous fistula was noted in the superior segment of the left lower lobe draining into the left inferior pulmonary vein. Two-dimensional echocardiography done for the patient was normal. Abdominal ultrasonography was found to be normal. Routine blood investigations were normal.



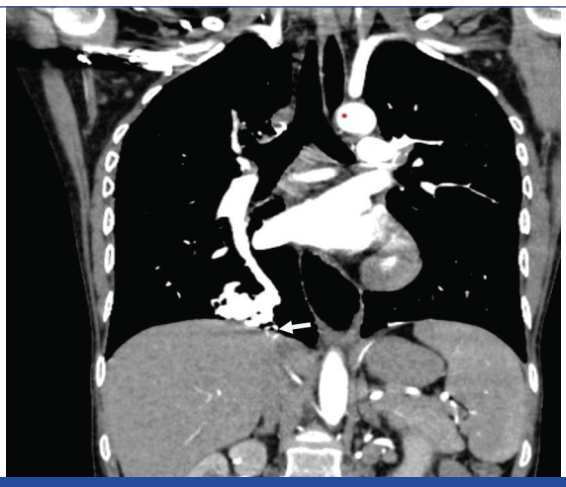
[Table/Fig-5]: Chest X-ray revealing right lower zone haziness.



[Table/Fig-6]: Contrast angiogram revealing right-sided Pulmonary AVM with non-specific interstitial changes with peripheral sparing (white arrow - AVM and the black arrows -interstitial changes).



[Table/Fig-7]: The 3D reconstructed image showing pulmonary AVM draining into pulmonary vein.



[Table/Fig-8]: Coronal image showing right AVM with branch from celiac artery.

The initial evaluation of the patient led to the diagnosis of SSc with ILD. Further evaluation of the patient showed the presence of Pulmonary AV Malformation (PAVM). There was no evidence of other visceral AVMs. The presence of telangiectasia along with Pulmonary AVM suggested a possible diagnosis of HHT. A revisit of the past medical history revealed the presence of recurrent and spontaneous epistaxis, a condition assumed by the patient to be less significant and not informed initially due to the familial nature of similar episodic epistaxis for three generations.

Hence, a final diagnosis of SSc with ILD and a rare association of HHT with pulmonary AVM was established.

Differential diagnosis: Even though the clinical presentation of the present case was highly suggestive of SSc, the possible differential diagnosis of SSc includes Eosinophilic fasciitis [2], scleredema adultorum buschke, scleromyxedema, rare possibilities like nephrogenic systemic fibrosis, occupation-related scleroderma mimics. Cutaneous amyloidosis can mimic scleroderma, and systemic amyloidosis presents rarely with Pulmonary Arterio Venous Malformations (PAVMS), but the absence of systemic involvement makes it implausible. The other possible causes of the co-existent pulmonary AVMs like post-congenital heart disease surgery, and hepatopulmonary syndrome were not correlating with the patient history, normal liver enzymes, and abdominal sonography [3,4].

The familial inheritance pattern of the disease and the bilateral nature of pulmonary AVMs with lower lobe preference, as in the present case, strongly suggest HHT as the diagnosis, compared to sporadic cases which present as single AVMs [5].

Treatment: The patient was started on Mycophenolate Mofetil (MMF) 500 mg once daily for seven days and was upgraded to twice daily doses on subsequent visits, also, started on methylprednisolone 16 mg twice daily. Tablet Diltiazem 30 mg thrice daily was started prophylactically to prevent renal crisis and Raynaud's phenomenon. Supportive care like nasal moisturiser, paraffin skin lotions, treatment for Gastroesophageal Reflux Disease (GERD), and contraceptive measures were also advised. The patient was planned for trans-catheter embolisation as CTPA revealed multiple tangled vessels measuring 3.3x3.7x3.3 cm draining into the right inferior pulmonary vein, but this procedure could not be done as the patient was not willing.

Outcome and follow-up: After starting immuno-modulator therapy, the patient tolerated the drugs well and was discharged. She is on follow-up and has been symptomatically better.

DISCUSSION

SSc is a rare chronic autoimmune CTD characterised by fibrosis, skin tightening, and microvascular injury to multiple organs. The presentation of this disease may be limited or diffuse. Diffuse cutaneous SSc has generalised involvement, ILD, severe arthralgia, and anti-Scl-70 positivity, as seen in the present patient [6].

Eosinophilic fasciitis presents with symmetrical pain and swelling of limbs followed by induration and joint contractures, with skin features that mimic SSc, but the absence of eosinophilia and hypergammaglobulinemia rules it out [2]. Scleredema adultorum Buschke may have features of SSc due to involvement of skin over the face and extremities, but predominant distal involvement, absence of diabetes, and failure of resolution over one year (as it usually occurs following *Streptococcal* infection and resolves over a year) make it less plausible. Scleromyxedema [7], a disease where dermal deposition of mucin with the proliferation of stellate fibroblasts and disordered collagen deposition, presents with dysphagia, arthralgia, and waxy papules symmetrically distributed over arms, hands, and face, which can have a similar presentation to SSc. However, this condition may be distinguished by the absence of telangiectasia, papules, and normal thyroid levels. Other rare possibilities like nephrogenic systemic fibrosis and diabetic chieroarthropathy can be included in the differential diagnosis due to the presence of shared clinical features like joint contractures and the absence of Raynaud's phenomenon. However, age at presentation, abdominal sonography, and other blood investigations help in differentiating it from our diagnosis. The absence of exposure to organic solvents, silica, and other chemicals rules out occupation-related scleroderma mimics [8].

According to the ACR-EULAR diagnostic criteria, a score of nine and above is diagnostic of SSc [1]. This case had a high positivity with a score of 16 according to this criterion, with the presence of skin thickening in all fingers of both hands extending proximal to metacarpophalangeal joints, presence of ILD, anti-Scl-70 positivity, fingertip pitting scar, and telangiectasia.

HHT, also known as Osler-Weber-Rendu disease, is a rare autosomal dominant genetic disorder characterised by AV malformations and telangiectasias [9]. The Curacao criteria, established by the HHT Foundation International, are useful for clinical diagnosis. Three or more of the following four criteria suggest a definite clinical diagnosis: 1) Spontaneous recurrent nosebleeds; 2) Mucocutaneous telangiectasia; 3) Visceral AVMs; 4) an affected first-degree relative [10].

Presently discussed patient fulfilled the first three criteria for the diagnosis of HHT, along with a family history of epistaxis. Most PAVMs are congenital, with 80-95% eventually manifesting with HHT. Studies have shown HHT to be present in 36% of patients with single PAVMs and 51-88% of patients with multiple PAVMs [11,12]. Pulmonary AVM draining into the inferior pulmonary veins with a feeding artery from the coeliac artery is a very rare presentation.

Effect of Pregnancy on HHT and Systemic Sclerosis (SSc) (The pregnancy link): The onset of symptoms after pregnancy in the present case correlates with both diseases. Pregnancy has been associated with an increased rate of PAVM growth and its associated complications [13]. Increased blood volume and cardiac output in pregnancy lead to increased pulmonary blood flow across low-resistance PAVMs, causing them to dilate. Secondarily, increased venous distensibility secondary to the progesterone effect causes augmentation of blood flow and increases PAVM size and associated complications [14]. Hence, the possibility of HHT in patients presenting with haemoptysis during pregnancy must be borne in mind. Conversely, scleroderma symptoms may also worsen with pregnancy, which is particularly noted in the first three years of the onset of scleroderma [15]. In the present case, the patient reported the onset and worsening of telangiectasia and skin changes in her first trimester, which progressed even after the abortion in the fourth month. Pregnancy with SSc is also considered to be a high-risk pregnancy, due to the high-risk of preeclampsia and kidney failure [16]. Hence, the patient was strictly advised contraception as it will have a deleterious effect on both diseases.

HHT and CTD Link: Even though there are few case reports, the association of HHT with CTDs and its pathogenesis has not been established. Kanchwala AA et al., reported a case of Rheumatoid arthritis with lung involvement in association with HHT in a middle-aged male patient [17] and suggested the possible association of the HHT gene product with CTDs. de Caravalho JF et al., also reported a similar case of Rheumatoid arthritis with HHT in an elderly female patient [18]. The authors emphasised the role of the TGF-β signaling pathway in both diseases. Jain D et al., reported a case of an elderly female who was diagnosed with HHT but also had associated ILD and calcinosis cutis [19]. The authors of the study suggested a possible need for serology testing for autoimmune antibodies in patients with HHT due to its unusual associations. Another study published in the Journal of Dermatology in Japan demonstrated HHT with dystrophic calcinosis cutis and retinal vascular lesions in an elderly female who had multiple telangiectasias [19]. However, no case of SSc has been found in association with HHT in an extensive review of the literature.

Pathophysiological Link of HHT and SSc: Based on the above reports, a plausible pathophysiological link between these two diseases can be understood. TGF-β is a pleiotropic growth factor that regulates the growth and differentiation of various cell types and immune regulation has been implicated in the pathogenesis of both HHT and SSc [20]. HHT is caused by decreased ENG and activin receptor-like kinase (ALK-1) genes, which are associated with TGF-β signaling [21]. TGF-β has also been studied to be an essential mediator for both fibrosis and vasculopathy in SSc [22].

The other pathogenetic mechanism common to both diseases is impaired nitric oxide-mediated vasodilation. In SSc, initial vascular insult due to various factors leads to endothelial cell activation and release of Endothelin 1 (ET-1), a potent vasoconstrictor. Transdifferentiation of these endothelial cells into mesenchymal cells with functional abnormalities results in impaired responsiveness to nitric oxide leading to vasoconstriction and tissue hypoxia [23]. In HHT, mutations in the ENG or ALK-1 gene are seen which interact with endothelial Nitric Oxide Synthase (eNOS) and regulate its activation. This leads to reduced ENG or ALK-1 protein in endothelial cells, eNOS uncoupling, and generation of Reactive Oxygen Species (ROS) instead of nitric oxide, leading to impaired nitric oxide-mediated vasodilation [24].

Henceforth, further research is needed to understand the role of the TGF-β pathway and nitric oxide in the pathophysiology of both diseases that may yield new therapeutic approaches for treatment.

CONCLUSION(S)

The present case report proposes a possible association of HHT with CTDs, especially scleroderma. The pathogenetic link between the two diseases could be the TGF-β and nitric oxide pathways. The role of antioxidants and their implications in the management of both diseases needs research. Even though rare, HHT has to be borne in mind as a differential diagnosis in pregnant females presenting with haemoptysis, which can be challenging as imaging requires radiation exposure.

REFERENCES

[1] Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747-55.
[2] Li JY. Eosinophilic Fasciitis. In: NORD guide to rare disorders. Lippincott Williams & Wilkins. Philadelphia, PA. 2003.
[3] Singh H, Khan YS. Pulmonary Arteriovenous Malformation (AVMs) (Archived). 2024. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/32644715/.
[4] Lange PA, Stoller JK. The hepatopulmonary syndrome. Ann Intern Med. 1995;122(7):521-29.
[5] Wong HH, Chan RP, Klatt R, Faughnan ME. Idiopathic pulmonary arteriovenous malformations: Clinical and imaging characteristics. Eur Respir J. 2011;38(2):368-75.
[6] Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(10103):1685-99.
[7] Vysakha KV, Poyuran R, Nair SS, Nair M. An unusual presentation of scleromyxedema as inflammatory myopathy. Acta Myol. 2019;38(1):13-16.
[8] Bobeica C, Niculet E, Craescu M, Parapiru EL, Corduneanu-Luca AM, Debita M, et al. Immunologic and non-immunologic sclerodermal skin conditions - Review. Front Immunol. 2023;14:1180221. Available from: https://doi.org/10.3389/fimmu.2023.1180221.
[9] Faughnan ME, Mager JJ, Hetts SW, Palda VA, Lang-Robertson K, Buscarini E, et al. Second international guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. Ann Intern Med. 2020;173(12):989-1001.
[10] McDonald J, Bayrak-Toydemir P, DeMille D, Wooderchak-Donahue W, Whitehead K. Curacao diagnostic criteria for hereditary haemorrhagic telangiectasia is highly predictive of a pathogenic variant in ENG or ACVRL1 (HHT1 and HHT2). Genet Med. 2020;22(7):1201-05.
[11] Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: Long-term results in 112 patients. J Vasc Interv Radiol. 2004;15(5):451-56.
[12] Pollak JS, Saluja S, Thabet A, Henderson KJ, Denbow N, White RI Jr. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. J Vasc Interv Radiol. 2006;17(1):35-44.
[13] Ference BA, Shannon TM, White RI Jr, Zawin M, Burdge CM. Life-threatening pulmonary haemorrhage with pulmonary arteriovenous malformations and hereditary haemorrhagic telangiectasia. Chest. 1994;106(5):1387-90.
[14] Khurshid I, Downie GH. Pulmonary arteriovenous malformation. Postgrad Med J. 2002;78(918):191-97.
[15] Steen VD. Scleroderma and pregnancy. Rheum Dis Clin North Am. 1997;23(1):133-47.
[16] Lazzaroni MG, Crisafulli F, Moschetti L, Semeraro P, Cunha AR, Neto A, et al. Reproductive issues and pregnancy implications in systemic sclerosis. Clin Rev Allergy Immunol. 2023;64(3):321-42.
[17] Kanchwala AA, Awan O, Javiad M. Coexistence of hereditary haemorrhagic telangiectasia and rheumatoid arthritis in a young man with normal parental genotype. Chest. 2009;136(4):20. Available from: https://doi.org/10.1378/chest.136.4_MeetingAbstracts.20S-d.
[18] de Carvalho JF, Maia Rodrigues CE, de Freitas Zerbini CA, Churilov LP. Rheumatoid arthritis associated with rendu - osler - weber disease: Second description. Vestnik of Saint Petersburg University. Medicine. 2021;16(3):147-52. Available from: https://doi.org/10.21638/spbu11.2021.301.
[19] Jain D, Viswanathan S, Ramasamy C. Hereditary hemorrhagic telangiectasia with unusual associations. Cureus. 2015;7(6):e278. Doi: 10.7759/cureus.278. PMID: 26180702; PMCID: PMC4494561.
[20] Komai T, Okamura T, Inoue M, Yamamoto K, Fujio K. Re-evaluation of pluripotent cytokine TGF-β3 in immunity. Int J Mol Sci. 2018;19(8):2261.
[21] Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. Eur Respir J. 2009;33(5):1186-94.
[22] Ayers NB, Sun CM, Chen SY. Transforming growth factor-β signalling in systemic sclerosis. J Biomed Res. 2018;32(1):03-12.
[23] Adigun R, Goyal A, Hariz A. Systemic Sclerosis (Scleroderma). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430875/.
[24] Jerkic M, Letarte M. Contribution of oxidative stress to endothelial dysfunction in hereditary haemorrhagic telangiectasia. Front Genet. 2015;6:34. Doi: 10.3389/fgene.2015.00034. eCollection 2015.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Respiratory Medicne, Sir Gangaram Hospital, New Delhi, India.
2. Consultant Pulmonologist, Department of Respiratory Medicne, Kauvery Hospital, Chennai, Tamil Nadu, India.
3. Professor, Department of Respiratory Medicne, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
4. Assistant Professor, Department of Respiratory Medicne, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Subramanian Suriyan,
118, Krithika Nivas, Ananthanathan Nagar, Mannivakkam Extension,
Chennai-602301, Tamil Nadu, India.
E-mail: drssmani@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 04, 2024
- Manual Googling: Apr 11, 2024
- iThenticate Software: Jun 03, 2024 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 04, 2024**
Date of Peer Review: **Apr 12, 2024**
Date of Acceptance: **Jun 04, 2024**
Date of Publishing: **Jul 01, 2024**