A case report on uneventful anticoagulation and persistence of type1 respiratory failure post severe COVID-19 infection in a patient of Osler-Weber-Rendu Syndrome.

Sachin Gautam

Maulana Azad Medical College

Govind Mawari

Maulana Azad Medical College

Mradul Kumar Daga (✉ drmraduldaga@gmail.com)

Maulana Azad Medical College <https://orcid.org/0000-0001-7774-7602>

Naresh Kumar

Maulana Azad Medical College

Research Article

Keywords: Osler-Weber-Rendu Syndrome, Hereditary hemorrhagic telangiectasia, HHT, Prophylactic Anticoagulation, Covid-19, SARS-CoV-2

Posted Date: October 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-941184/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Ever since the WHO's declaration of the SARS-CoV-2 pandemic, the medical literature has been focusing upon the patterns of association of SARS-CoV-2 with different diseases. Patients with Osler-Weber-Rendu Syndrome, also known as, Hereditary hemorrhagic telangiectasia (HHT), presents with recurrent epistaxis, nostril manipulations, incidental detection of multiple AVMs (Arterio-Venous Malformations), and telangiectasias over mucocutaneous tissues and internal organs. In addition, these AVMs are prone to bleed or act as a nidus for thrombus formation apart from other serious complications like chronic hypoxemia, anemia, pulmonary artery hypertension, heart failure, and cerebrovascular disease accidents. Here, we provide a case report of such a patient who was diagnosed with HHT as per 'Curaçao criteria'; having a history of multiple episodes of epistaxis, radiological evidence of AVMs over left calf, pulmonary and hepatic region, multiple telangiectasias in the splenic region and uterine vascular malformations. Upon acquiring severe COVID-19 infection, the patient developed complications like anemia, pulmonary artery hypertension, sepsis, acute kidney injury, and post COVID-19 persistence of type1 respiratory failure. Moreover, the risk-benefit ratio of anticoagulation therapy in such patients with COVID-19 infection is tricky and challenging; however, our patient was prophylactically anti-coagulated with enoxaparin for 12 days with an uneventful outcome. Keywords: Osler-Weber-Rendu Syndrome, Hereditary hemorrhagic telangiectasia, HHT, Prophylactic Anticoagulation, Covid-19, SARS-CoV-2.

Introduction

Osler-Weber Rendu syndrome, also known as, Hereditary hemorrhagic telangiectasia (HHT), is a rare genetic disorder inherited as an autosomal dominant trait. The disorder is characterized by recurrent epistaxis, telangiectasias, and multiple arteriovenous malformations involving different body systems, including mucocutaneous sites. It has an estimated prevalence of 10-20 per 100,000 individuals [1]. These vascular malformations are genetic angiodyplasia which is fragile and prone to thrombosis and bleeding. Due to frequent epistaxis and nostril manipulation, these patients can catch COVID-19 infection [2]. Here, we provide a case report of a patient diagnosed with HHT as per 'Curaçao criteria,' who, upon acquiring severe COVID-19 infection, became symptomatic and developed multiple complications with the further need of anticoagulation therapy.

Case Report

A 45 years old female patient presented to our emergency department with complaints of shortness of breath for the past eight days, gradually progressive, exertional in nature without orthopnea and paroxysmal nocturnal dyspnea, cough with sputum production for five days, and two episodes of epistaxis in the past one day, which got relieved on pinching the nose. She also complained of dull aching, nonspecific abdominal pain in the past one month in the right upper abdominal region, and a history of long-standing swelling over the left calf region that has increased since one month. There was no history of chest pain, hemoptysis, fever, pedal edema, burning micturition, and bowel abnormality. She was not a known case of hypertension and diabetes. Her past history was suggestive of chullah exposure

for 30 years, old treated pulmonary tuberculosis 20 years back, had multiple episodes of epistaxis since childhood period, not severe enough to require a blood transfusion, which got relieved on its own and repeated hospital visits due to pulmonary symptoms. Family and personal history were insignificant; however, she had recently been prescribed a salbutamol metered-dose inhaler (MDI) on an SOS basis. On presentation, her blood pressure was 124/84 millimeters of mercury, pulse rate of 105 / min in the right radial artery, respiratory rate of 17 /min, the random blood sugar of 213 mg/dL, and oxygen saturation of 92% under ambient air. On general physical examination, she was afebrile, pallor was noticed on lower palpebral conjunctiva, clubbing, hexadactyly of bilateral feet was noted, and hemorrhagic lesions were noted in bilateral hands and upper chest of the patient, Fig (1). A swelling was also noted in the left leg over the calf region, soft and pulsatile, with an audible bruit heard over auscultation.

On systemic examination, bruits were heard over the right inframammary, interscapular, and tricuspid area, bilateral coarse crepitations over the infra scapular area were noted, and mild tenderness was also noted in the right hypochondrium area, and the rest of the systemic examination was within normal limits. Patients' electrocardiograph was suggestive of right ventricular strain, right axis deviation, and 'p' pulmonale with sinus tachycardia, and a chest radiograph was suggestive of bilateral lower respiratory tract infection with query right lower and middle zone mass lesion (fig2). An arterial and venous doppler was performed, which showed an A-V malformation with no thrombus over the left calf region. The patient's routine blood parameters and RT-PCR swab (nasopharyngeal and oropharyngeal) for SARS-CoV-2 were sent along with ABG (arterial blood gas), which showed type 1 respiratory failure. Patients' deranged blood parameters have been tabulated in the table (table1); however, liver function tests, serum creatine phosphokinase-total/MB fraction, sodium, potassium, amylase, and lipase remained within normal limits during the further course of hospital stay and her serology for HIV, hepatitis B, and C was negative. On admission, a provisional diagnosis of bilateral lower respiratory tract infection with a COVID-19 suspect with query pulmonary artery hypertension with query right lung mass lesion with query heart failure was made. Patients' blood and urine cultures and sputum for gram stain, acid-fast bacilli, fungal stain, and culture and sensitivity were collected and sent for analysis before augmenting intravenous antimicrobials. The patient's treatment began with oxygen support via venturi mask at 6 liters per minute, intravenous antibiotics as injectable ceftriaxone and tablet azithromycin, and blood transfusion of one unit of packed cell volume because of iron deficiency anemia. On the second day, her 2-D Echo and Contrast-Enhanced Computed Tomography (CECT) of chest and abdomen along with angiography (CT Angio) were performed. Transthoracic 2-D Echo showed a normal echo study with 60% ejection fraction, and CT Angio of the chest with the abdomen (Fig 3.) showed pulmonary artery hypertension with multiple pulmonary arteriovenous malformations in the right middle and bilateral lower lobes with hepatic, splenic, and uterine arteriovenous malformations and telangiectasia feature suggestive of Rendu-Osler-Weber Syndrome. Patients' RT-PCR for SARS-CoV-2 reported positive; hence the patient was transferred to COVID-ICU with the addition of intravenous steroids as methylprednisolone and prophylactic anticoagulation with LMWH (lower molecular weight heparin), enoxaparin, at a dose of 0.5mg/kg subcutaneously daily, with regular monitoring of PT/INR (prothrombin time/ International Standardized Ratio), in the treatment. During the further course of hospital stay, the patient's respiratory discomfort increased, and her oxygen

requirement increased, oxygen saturation dropped to 86% on room air, and ABG showed paO₂ of 71 mmHg (83 – 108mmHg) around the fifth day; hence she was shifted to BIPAP (Bilevel Positive Airway Pressure) noninvasive mode of ventilation. The same day, blood investigations showed sepsis with acute kidney injury (table1); hence her antibiotics were upgraded to injection piperacillin-tazobactam combination in renal modified doses and linezolid. However, her blood, urine, and sputum cultures were reported as sterile. The patient stayed for 12 days in ICU, where she received one more unit of packed cell volume and injection meropenem along with prophylactic anticoagulation with enoxaparin, after which she was transferred back to ward on intermittent BIPAP support for 12 hours daily with NRB (Non rebreathing mask) at 10-12 liters per minute of oxygen support, as she reported negative for SARS-CoV-2. After stabilizing her in the ward for three more days and counseling her for further evaluation of the disease in the pulmonary department, the patient requested discharge on home-based long-term oxygen support because of persistence of type 1 respiratory failure as post-COVID-19 sequelae. Written informed consent was taken from the patient and her relatives for presenting her clinical data

Discussion

HHT has been linked to mutations in any one of three genes: ENG, ACVRL1, or SMAD4 [3].

The diagnostic criteria for HHT, 'Curaçao criteria,' was developed in 1999 consisting of four entities: 1) Nosebleeds: which can be spontaneous or recurrent, 2) Telangiectatic lesions: at multiple locations like lips, oral cavity, fingertips, and nasal mucosa, 3) Presence of visceral lesions: GI telangiectasia, pulmonary, hepatic, cerebral, and spinal AVMs and 4) Family history of the first-degree relative with HHT. A definitive, possible, or uncertain diagnosis is considered if any three, two, or less than two of the criteria mentioned above are met, respectively.[4]. However, our patient did not have a positive family history, although she did have a history of epistaxis since childhood, which was not severe, and recovered independently, just like her past episodes. Moreover, epistaxis is the most common symptom of HHT, appearing as early as before 20 years of age with almost 90% presence by 40 years of age [5]. Nosebleeds and incidental detection of A-V malformation over the left calf region along with pulmonary, hepatic, and splenic malformation and telangiectasias on CT angiography of chest and abdomen confirmed the diagnosis. These vascular malformations are genetic angiodysplasia which is fragile and prone to thrombosis and bleeding. The Pulmonary A-V malformations (PAVM) show a female predominance with a varied presentation from asymptomatic to serious complications like development of right- to- left shunt leading to hypoxemia, paradoxical embolism resulting in cerebral stroke as well as cerebral abscess, neurological deficits, and massive hemoptysis [6][7]. As per "Pollak JS and colleagues," 70%-90% of patients with PAVM are associated with Rendu Osler Weber syndrome [8]. However, the incidence of PAVM in patients with HHT is around 30% [9]. Pulmonary artery hypertension was seen in our patient due to dilatation of the main, right, and left and pulmonary artery, measuring ~3.4cm,2.3cm, and 2.2 cm, respectively, along with dilatation of hepatic veins and suprahepatic IVC. These findings could be attributed to A-V shunting in the liver leading to high cardiac output or due to idiopathic pulmonary artery hypertension or due to PAVMs [10]. The occurrence of telangiectasias and A-V malformations in the GI (gastrointestinal) tract apart from skin makes the patient vulnerable to bleed

even more; as mentioned in the literature, internal GI tract telangiectasias can bleed in one-third of patients [11]. In addition, both epistaxis and GI telangiectasias can lead to anemia, as in our patient, it was present, but no evidence of bleeding from anywhere. However, the real importance of our case lies in the fact that her RT-PCR for SARS-CoV-2 reported positive, making her a high-risk patient even more. Due to frequent epistaxis and nostril manipulation, these patients can catch COVID-19 infection [2]. Apart from this, complications like hypoxemia, pulmonary AVMS, anemia, and history of pulmonary tuberculosis superimposed to COVID-19 as in our patient, could result in a guarded prognosis of the patient [2]. Moreover, our patient did land in the severe COVID-19 category as per MoHFW (Ministry of Health and Family Welfare) guidelines on the clinical severity of COVID-19 infection in India, along with raised inflammatory markers [12]. On the contrary to this, a study by “Marcos S et al.” showed that COVID-19 infection was acquired in 25 of 138 patients with HHT, had a milder course, without raised inflammatory markers, and better clinical outcome [13]. However, our patient did experience complications like sepsis and acute kidney injury, which responded well to treatment. Not to forget that patients of COVID-19 are at a higher risk of thrombosis [2], and prophylactic anticoagulation in patients of HHT with severe COVID-19 infection is quite challenging and could have unfavorable outcomes. A meta-analysis by “Umemura Y and colleagues” found that anticoagulation may be tried in such patients with close monitoring by the physician [14]. On the contrary, few studies have found increased epistaxis and GI bleeding episodes on anticoagulating such patients [15]. Furthermore, the risk-benefit ratio of such anticoagulation therapy in HHT patients with COVID-19 infection is understudied. However, prophylactic anticoagulation with 0.5mg/kg of enoxaparin subcutaneously once daily amounting to ~ 50mg daily was done in our case for 12 days in ICU as per AIIMS (All India Institute of Medical Science) COVID-19 management guidelines, which state to use 0.5mg/kg of enoxaparin subcutaneously twice daily in severe patients [16]. Although our patient was a high-risk candidate for bleeding, however no thrombosis or bleeding was observed. Upper abdominal discomfort in our patient could be due to hepatic or splenic involvement. As per literature, the involvement of hepatic AVMs is 30%, which could lead to portal hypertension, biliary disease, and high output cardiac failure [17]. Although splenic involvement in patients with HHT is rare and asymptomatic, in a case report by “Takamatsu S, Sato K,” splenectomy was performed because of hypervascular lesions in the spleen due to persistent upper abdominal pain [18]. However, abdominal discomfort was relieved in our patient. The persistence of type 1 respiratory failure and requirement of long-term oxygen therapy in our patient could be attributed to post COVID-19 infection sequelae as most HHT patients without superimposed SARS-CoV-2 infection otherwise exhibit a paO_2 of 80 mmHg on room air [19]. At last, we would like to conclude with an advisory issued by “the North American cure HHT scientific and medical advisory council,” where they have mentioned the need for escalation of vaccination even among patients with HHT, with no reason of believing blood clots formation post vaccination amongst them [20].

Conclusion

Incidental detection of Osler-Weber-Rendu Syndrome, also known as HHT (Hereditary hemorrhagic telangiectasia) with severe COVID-19 infection could exaggerate the complications arising from the

syndrome and infection itself, hence making them high-risk patients for COVID-19. Furthermore, clinicians should be aware of such patients and the risk-benefit ratio of anticoagulation among such patients during the COVID-19 crisis.

Declarations

- **Declaration of patient consent:** The all authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
- **Funding:** No organized funding source was used in study conduction.
- **Acknowledgements:** None
- **Conflict of interests:** The all authors declare that they have no conflict of interest.
- **Consent to participate:** written consent was taken from all participating subjects.
- **Consent for publication:** all the authors give their consent for publication of the manuscript
- **Code availability:** not applicable
- **Author contributions:**

Sachin Gautam (S.G), Govind Mawari¹(G.M), Mradul Kumar Daga (M.K.D), Naresh Kumar (N.K)

M.K.D., G.M and S.G.; Designed, Supervised and planned the research. M.K.D, G.M, N.K and S.G; performed the Patient Examination and lab experiments G.M, and S.G; collected the data M.K.D, G.M, and S.G; took the lead in writing the manuscript. M.K.D, G.M, N.K, and S.G; Final manuscript editing

All authors provided critical feedback and helped shape the research, analysis and manuscript.

References

1. Nikolaou I, Rafailidis V, Kartas A, et al. A case of pulmonary arteriovenous malformation in the setting of Rendu Osler Weber syndrome. Radiology case reports. 2020;16(3):483–6. <https://doi.org/10.1016/j.radcr.2020.12.024>.
2. Topping PM, Brusgaard K, Ousager LB, et al. National mutation study among Danish patients with hereditary haemorrhagic telangiectasia. Clin Genet. 2014;86(2):123–33. <https://doi.org/10.1111/cge.12269>.
3. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91(1):66–7. [https://doi.org/10.1002/\(sici\)1096-8628\(20000306\)91:166::aid-ajmg123.0.co;2-p](https://doi.org/10.1002/(sici)1096-8628(20000306)91:166::aid-ajmg123.0.co;2-p).

4. Plauchu H, de Chadarevian JP, Bideau A, et al. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet.* 1989;32(3):291–7. <https://doi.org/10.1002/ajmg.1320320302>.
5. Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. *J Med Genet.* 1992;29(8):527–30. <https://doi.org/10.1136/jmg.29.8.527>.
6. Wang KY, Chen JC, Hsu JY. Osler-Weber-Rendu syndrome complicated with pulmonary arteriovenous malformation: A case report and review of literatures. *J Med Sci [serial online]* 2015 [cited 2021 Sep 18];35:131-4. Available from: <https://www.jmedscindmc.com/text.asp?2015/35/3/131/158695>.
7. Kjeldsen AD, Oxhøj H, Andersen PE, et al. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. *Chest.* 1999;116(2):432–9. <https://doi.org/10.1378/chest.116.2.432>.
8. Pollak JS, Saluja S, Thabet A, et al. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. *Journal of vascular interventional radiology: JVIR.* 2006;17(1):35–45. <https://doi.org/10.1097/01.RVI.0000191410.13974.B6>.
9. Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia. *N Engl J Med.* 1995;333(14):918–24. <https://doi.org/10.1056/NEJM199510053331407>.
10. Cottin V, Dupuis-Girod S, Lesca G, et al. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (rendu-osler disease). *Respir Int Rev Thorac Dis.* 2007;74(4):361–78. <https://doi.org/10.1159/000103205>.
11. Kjeldsen AD, Kjeldsen J. Gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. *Am J Gastroenterol.* 2000;95(2):415–8. <https://doi.org/10.1111/j.1572-0241.2000.01792.x>.
12. Gaetani E, et al. Hereditary haemorrhagic telangiectasia: A disease not to be forgotten during the COVID-19 pandemic. *Journal of thrombosis haemostasis: JTH* vol. 2020;18(7):1799–801. doi:10.1111/jth.14885.
13. Updated clinical management protocol on covid19 [Internet]. *Mohfw.gov.in.* 2020 [cited 9 November 2020]. Available from: <https://www.mohfw.gov.in/pdf/UpdatedClinicalManagementProtocolforCOVID19dated03072020.pdf>.
14. Marcos S, Albiñana V, Recio-Poveda L, et al. SARS-CoV-2 Infection in Hereditary Hemorrhagic Telangiectasia Patients Suggests Less Clinical Impact Than in the General Population. *Journal of clinical medicine.* 2021;10(9):1884. <https://doi.org/10.3390/jcm10091884>.
15. Umemura Y, et al. Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials. *Journal of thrombosis haemostasis: JTH* vol. 2016;14(3):518–30. doi:10.1111/jth.13230.
16. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* vol. 2001;286:1869–78. doi:10.1001/jama.286.15.1869. 15) .

17. Begbie ME, Wallace GM, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgraduate medical journal* vol. 2003;79(927):18–24. doi:10.1136/pmj.79.927.18.
18. Takamatsu S, Sato K, Kato S, et al. Splenic Involvement in Hereditary Hemorrhagic Telangiectasia. *Case reports in medicine*. 2016;2016:3212947. doi:10.1155/2016/3212947.
19. Dines DE, Arms RA, Bernatz PE, et al. (1974). Pulmonary arteriovenous fistulas. *Mayo Clinic proceedings*, 49(7), 460–465.
20. Scott Olitsky. should people with HHT be concerned about receiving a COVID-19 vaccine? Update: May 13, 2021 | COVID-19 VACCINATIONS & BLEEDING <https://curehht.org/covid19-updates/#bleeding>.

Tables

riables with erence range	Day 1st	Day 5th	Day 12th	Day 18th	Day 20th
moglobin	7.3	8.7	10.8	11.2	11.0
tal Leukocyte unt (5000-10,000 ls/ mm ³	12300	29700	18300	14600	10200
fferential leukocyte unt (60-75% lymorphs,20-40% aphocytes, onocytes 2-6%	76/18/4/2	93/4/2/1	90/7/2/1	82/14/3/1	72/23/4/1
platelets	230000	430000	340000	410000	365000
ea/ Creatinine	37/0.6	87/1.7	65/1.2	45/0.9	33/0.9
erleukin-6 level 7pg/ml)	1.5	23			
rritin	788	832	713	645	690
ghly sensitive eactive protein 5mg /L)	18	68	43	16	
ocalcitonin (0.0-0.5 /ml)	0.4	2.1	0.9	0.04	
ype natriuretic ptide (BNP)	65	900	476		
Dimer	341	556	701	476	389
rum lactate ydrogenase (125- 6 U/L)	380	447	410	357	
ernational ormalized Ratio (0.9	0.9	1.0	0.9		

1.1)					
ood, Urine culture d sputum culture routine and fungal ments.	STERILE	STERILE			
ine-routine icroscopy	No abnormality detected	No active sediments with non- glomerular proteinuria +. rest within normal limits	Proteinuria +, rest within normal limits		
terial blood gas					
(7.350 - 7.450)	7.413	7.367	7.39	7.421	7.418
2 (83 – 108mmHg)	79	72	73.5	75.2	77.6
o ₂ (35-45mmHg)	37	40	38	36.2	38.7
o ₃ ⁻ (22 -26mmol/L)	25	22.3	24.7	22.4	23.3
ctate (0.5 – mmol/L)	1.7	2.9	2.2	1.1	0.8

Deranged blood parameters during hospital stay. Po₂: **Partial pressure of oxygen**, Pco₂: **Partial pressure of carbon dioxide** and HCO₃⁻: **Bicarbonate**

Figures

Figure 1

Clinical features [A], [C] and [D]: Telangiectasias over face, forearm and upper chest and neck region. [D]: showing pallor and clubbing.

Figure 2

chest radiograph showing right lower zone and middle zone consolidation, query mass lesion, along with left middle zone haziness.

Figure 3

CE CHEST AND ABDOMEN ANGIOGRAPHY-[A]: Right upper pointer showing AVM with aneurysmal sac of size ~6.8(Tr) x 7(AP) x 7.2(CC) cm in right middle lobe. Another AVM with aneurysmal sac of size ~3.5(Tr) x 2.5(AP) x 2.7(CC) is highlighted by left lower pointer. [B] Pointer showing multiple hepatic telangiectasias in bilateral lobes along with hepatomegaly of ~19.5cm.[C] Pointer showing hepatic AVM of size 0.9 x 1.4 cm. [D] Pointer showing splenic telangiectasia appearing as a hyper-enhancing nodule of size ~0.5x0.6 cm along with dilated and tortuous splenic artery.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklist.docx](#)