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.

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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 angiodysplasia 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 audile 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 send along with ABG (arterial blood gas), which showed type1 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 Render-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 stoke 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 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
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.
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- **Author contributions:**

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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.

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### Tables
| Variables with reference range | Day 1st | Day 5th | Day 12th | Day 18th | Day 20th |
|--------------------------------|---------|---------|----------|----------|----------|
| Hemoglobin                     | 7.3     | 8.7     | 10.8     | 11.2     | 11.0     |
| Total Leukocyte count (5000-10,000/µm³) | 12300   | 29700   | 18300    | 14600    | 10200    |
| Differential leukocyte count (60-75% lymphs, 20-40% lymphocytes, 2-6% monocytes) | 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   |
| Serum Creatinine               | 37/0.6  | 87/1.7  | 65/1.2   | 45/0.9   | 33/0.9   |
| Interleukin-6 level (7pg/ml)   | 1.5     | 23      |          |          |          |
| ferritin                       | 788     | 832     | 713      | 645      | 690      |
| Highly sensitive reactive protein (5mg/L) | 18      | 68      | 43       | 16       |          |
| Calcitonin (0.0-0.5 µg/ml)     | 0.4     | 2.1     | 0.9      | 0.04     |          |
| Type natriuretic peptide (BNP) | 65      | 900     | 476      |          |          |
| Dimer                          | 341     | 556     | 701      | 476      | 389      |
| Serum lactate hydrogenase (125-3 U/L) | 380     | 447     | 410      | 357      |          |
| International normalized Ratio (0.9) | 0.9 | 1.0     | 0.9      |          |          |
1.1) 

| Procedure                                  | STERILE | STERILE |           |           |           |
|--------------------------------------------|---------|---------|-----------|-----------|-----------|
| Blood, Urine culture                       |         |         |           |           |           |
| sputum culture                             |         |         |           |           |           |
| routine and fungal cultures                |         |         |           |           |           |
| R. stercrocy                              | No      | No      | Proteinuria | +, rest  | within  |
|    routine                                | abnormality | active  | normal    | limits    | normal    |
|    cyroscopy                              | detected | sediments| limits    | limits    | limits    |
|    +, rest within normal limits           |         |         |           |           |           |

| Serial blood gas                           | 7.413   | 7.367   | 7.39      | 7.421     | 7.418     |
| (7.350 - 7.450)                            |         |         |           |           |           |
| Po2 (83 - 108mmHg)                         | 79      | 72      | 73.5      | 75.2      | 77.6      |
| C02 (35-45mmHg)                            | 37      | 40      | 38        | 36.2      | 38.7      |
| O3 (22-26mmol/L)                           | 25      | 22.3    | 24.7      | 22.4      | 23.3      |
| Cate (0.5 - 5mmol/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.

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