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Case Report

Hypovolemic Shock Associated with Post-COVID-19 Syndrome in a Patient with Hereditary Hemorrhagic Telangiectasia: Case Report

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Abstract

Introduction: Coronavirus disease (COVID-19) caused by SARS-CoV-2, has been a pandemic that has affected millions of people worldwide, which after infection is capable of leaving significant sequelae, currently known as post-COVID-19 syndrome. On the other hand, Hereditary Hemorrhagic Telangiectasia (HHT), also called Rendu-Osler-Weber (ROW) syndrome, is a multisystemic vascular disorder characterized by arteriovenous malformations and mucocutaneous telangiectasias that clinically manifest with spontaneous epistaxis, gastrointestinal bleeding, among others. **Material and Methods:** This case report describes a patient with Rendu-Osler-Weber syndrome who, after infection with SARS-CoV-2, developed massive hemorrhagic complications (hypovolemic shock) that had not been present during the course of her disease. **Discussion:** It is important to keep in mind that SARS-CoV-2 infection in patients with Rendu Osler Weber syndrome leads to an increased risk of massive bleeding; however, this association is not yet well established, so this clinical case describes this phenomenon.

Keywords: Hereditary hemorrhagic telangiectasia; Rendu-Osler-Weber syndrome; Arteriovenous malformations; Haemorrhage; COVID -19; Post-COVID-19 syndrome; Hypovolemic shock

Introduction

Hemorrhagic shock can be defined as massive blood loss that will lead to a decrease in oxygen supply at the cellular level, which is insufficient to meet the demand of aerobic metabolism. It is classified in 4 degrees and takes into account the amount of blood lost, vital signs, clinical and neurological characteristics of the patient [1,2]. Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler-Weber syndrome is a rare multisystemic disease, which causes the aberrant formation of some blood vessels, is autosomal dominant with variable penetrance [3,4]. The prevalence of HHT varies between 1.5 to 2 persons per 10,000 inhabitants, it is estimated that this disease is an underdiagnosed condition, and usually has a long delay in the protocolization of patients due to the rarity of the disease [5]. More than 600 genetic mutations have been described as a cause of this disease, however 3 genes are

the main triggers, among which the ENG gene, ACVRL1 (also known as ALK1) and MADH4 (also known as SMAD4) stand out. All of these aforementioned genes encode proteins that belong to the TGF-β signaling pathway [6]. The ENG gene is located on chromosome 9q34 and encodes the endoglin protein (CD105), being the first gene where mutations were identified, it is known as HHT type 1 (HHT1). Endoglin is a glycoprotein that functions as a endothelial receptor and together with ALK1, participate in the signaling pathway of Transforming Growth Factor (TGF)-β [7,8]. The ACVRL1 gene located on chromosome 12q13 encodes only activin receptor-like kinase 1 (ALK1), defects in this gene result in HHT type 2 (HHT2). Last but not least there are mutations in the MADH4 gene (encoding the SMAD4 protein), a transcription factor that mediates signal transduction in the TGF-β pathway and is associated with the development of juvenile polyposis overlap-HHT (JPHT) syndrome which accounts for approximately 1% of HHT cases [4,9,10]. These proteins are essential for angiogenesis, integrity, vascular remodelling, as well as for the migration and proliferation of muscle cells; however, when there is a haploinsufficiency due to mutation of these proteins, normal endothelial formation, structure and response are altered. However, the expression of HHT symptoms is related to the age and penetrance of the disease, and these symptoms worsen with the passage of time [3,4].

The main clinical manifestation is mucocutaneous telangiectasias, which can be found at the nasal level in up to 90% of patients, causing recurrent and spontaneous epistaxis [11]. However, these same lesions can be observed on the face, conjunctivae, auricular pavilions, lips, tongue, oral mucosa, arms, hands (especially on distal phalanges) and even feet. They appear as small red- violaceous spots 1-3 mm in diameter, pulsatile and chronically they may converge and increase in size creating arborizing lesions [11,12]. In the gastrointestinal tract we can find these same malformations in up to one third of patients; they can appear in the stomach, small and large intestine, this being the etiology of gastrointestinal tract bleeding, which clinically presents with hematemesis or melena. It is important to consider that these patients tend to present various vascular malformations (AVM); including pulmonary (PVM), cerebral, hepatic and spinal malformations. These are aberrant connections that form between arteries and veins; therefore, they do not have an intermediate capillary system [13]. They are composed of an aneurysmal sac with one or more afferent feeding arteries and one or more efferent draining veins [7,9,14]. The diagnosis of this pathology should be based on the Curaçao clinical criteria, it will be definitive if 3 of the 4 criteria are present, it is considered possible or suspected if 2 criteria are present and unlikely if less than 2 criteria are present (Table 1). Although a definitive, diagnosis can be made by molecular genetic testing [15-17].

Curacao Criteria.
Epistaxis: spontaneous and recurrent nosebleeds.
Telangiectasias: the most common sites include the lips, oral cavity, palms, toes and nose.
Visceral injuries including gastrointestinal AVMs, hepatic AVMs, cerebral AVMs (CAVMs) or spinal AVMs
Family history: one first-degree relative with HHT according to these criteria.

Table 1: Curaçao clinical criteria.

COVID-19 is a multisystemic pulmonary disease caused by the SARS-CoV-2 virus. The clinical manifestations of this pathology range from asymptomatic patients, headache, fever, dyspnoea, cough, anosmia/ageusia, myalgia, respiratory failure and multiorgan failure. However, it is important to highlight the disability that this disease can cause, causing important complications after recovery, thus encompassing an endless number of symptoms that we call post-COVID-19 syndrome [18,19]. Post-COVID- 19 syndrome is increasingly recognized as a clinical entity characterized by symptoms that persist for more than 3 weeks after the diagnosis of COVID-19. Its incidence varies from 10 to 35% of cases, yet it has been shown that up to 85% of hospitalized patients present with post-COVID-19 syndrome.19 However, there is currently no worldwide consensus on the definition and classification of post-COVID-19 syndrome. The pathogenesis of post-COVID-19 syndrome is still under investigation, so that the cornerstone of these complications is based on prolonged inflammation. Within this context, several interleukins are involved, most notably IL-4 and IL-6, which have the ability to penetrate the blood-brain barrier and disrupt CNS homeostasis, thus contributing to possible neurological complications. A COVID-19-associated inflammation could lead to a decrease in IL-6-mediated GABA receptors, thus explaining chronic neuromotor and cognitive fatigue. The cytokine storm is accompanied by activation of the sympathetic system and in turn, excessive release of catecholamines, which further conditions increased production of IL-6 and other cytokines, exponentially increasing multi-organ inflammation [20,21].

To date, more than 55 long-term clinical manifestations that characterize post-COVID-19 syndrome have been identified and it is estimated that 80% of infected patients develop 1 or more symptoms, including fatigue (58%), headache (44%), attention deficit disorder (27%), hair loss (24%), dyspnoea (24%) [22-24]. Although it is well known that COVID-19 causes a state of hypercoagulability, leading to thrombotic events, there are some other pathophysiological factors that can cause bleeding at any time throughout the disease, as well as in the recovery phase, such as thrombocytopenia, a hyper fibrinolytic state, the consumption

of coagulation factors and the administration of anticoagulants as a thromboprophylactic measure. Other causes have been proposed, such as cytokine storm, prolonged frank tissue hypoxia and direct virus invasion into the affected tissues causing tissue damage [25].

Material and Methods

To describe the association that exists in patients with Rendu Osler Weber syndrome who had COVID-19 and have an increased risk of haemorrhage.

Results

A 70-year-old female patient was admitted to the Emergency Department for presenting spontaneous epistaxis, as well as hematemesis on 2 occasions and an episode of syncope, with unquantified losses of approximately 2500 cc, accompanied by asthenia, adynamia, anosmia and dysgeusia of 1 month of evolution. On arrival, vital signs were reported: BP 93/62 mmHg, heart rate 120 bpm, respiratory rate 24 rpm, temperature 36.5°C, Sat 89% O_2. On physical examination on admission the patient was found to be of chronological age, awake, conscious, oriented in space, time and person, Glasgow 14 points, higher mental functions preserved, isochoric pupils normoreflexic, marked tegumentary pallor, face with presence of mucocutaneous telangiectasias with predominance in the malar region, of red-violet coloration of 0.5-1 cm, these are present in perioral region and tongue (predominantly in the dorsum) as well as in soft palate, dehydrated oral mucosa, hematic remains in oral cavity and nares, cylindrical neck without adenopathies or jugular ingurgitation data, normolinear thorax with increased respiratory movements, bilateral vesicular murmur present, no pleuropulmonary syndrome, rhythmic heart sounds increased in intensity and tone, without added murmurs, maintaining perfusory AT without vasopressor support. Soft depressible abdomen with moderate colicky pain on superficial and deep palpation in the epigastrium, negative ureteral stitches. Currently there is no evidence of active bleeding, rectal examination with a clean glove. Extremities intact, presence of petechiae in distal phalanges of both hands including feet, osteotendinous reflexes preserved, Daniels scale 3/5, delayed capillary filling.

She has a hereditary family history of father with Rendu-Osler-Weber syndrome, who died at the age of 50 years due to cerebral aneurysm, hypertensive mother, who died of hemorrhagic cerebrovascular disease at the age of 60 years, 4 siblings with Hereditary Hemorrhagic Telangiectasia proven by genetic methods. Personal pathological history of importance for the disease; Rendu-Osler- Weber syndrome since the age of 14 years in self- control, Diabetes type 2 for 28 years in treatment with NPH Insulin, Systemic Arterial Hypertension with 30 years of evolution in management with losartan, prazocin, metoprolol, Hypothyroidism for 40 years in treatment with levothyroxine, Surgical: rhinoseptoplasty 37 years ago without complications, total hysterectomy 31 years ago for uterine myomatosis without complications, allergies to nifedipine, transfusional denied. Positive PCR test for SARS-CoV-2 7 weeks prior to admission, without in-hospital management, treated with non-steroidal anti-inflammatory drugs, glucocorticoids and low molecular weight heparin.

Admission labs are takenreporting; Leukocytes 5.5 x10^3/uL, Erythrocytes 2.62 x10/uL^6, Hemoglobin 5.10 g/dL, Hematocrit 18.17 %, MCV 69.30 fL, MCH 19.46 pg, Platelets 190 x106, Neutrophils 79.2 %, Lymphocytes 13.2 %, Eosinophils 0.6 %, Tp 13.70 sec, TTP 32.80 sec, INR 1.26 sec, Serum Creatinine 1.1 mg/dL, Glucose 633 mg/dL, Urea 30.09 mg/dL, BUN 14.06 mg/dL. Arterial blood gases pH 7.49, pCO2 40 mmHg, pO2 36 mmHg, Htc20%, HCO3 29.8mmol/L, BE 6.6 mmol/L P/F 171 mmHg. Admitted to the Emergency Department with the diagnosis of hypovolemic shock of hemorrhagic type grade III ATLS, WHO grade IV anemia of microcytic type, hypochromic, upper gastrointestinal tract bleeding Glasgow-Blatchford 11 points, spontaneous epistaxis and uncontrolled type 2 diabetes. Diagnostic endoscopy was performed 3 days after hospital admission, which reported: esophagus with preserved morphology and distensibility, pale pink mucosal features throughout with the area of transition of the epithelia and hiatus at 40 cm from the ADS. Stomach with preserved morphology and distensibility with hiatus to retroversion lax, mucosa of the fundus body and antrum with areas of multiple vascular dysplasia alternating with whitish areas with moderate erythema . In the body there are polypoid lesions of 2 mm, covered with angiodysplasias, the pylorus is central and permeable to the passage of the endoscope, the gastric lake is hyaline in appearance. Duodenal bulb and 2nd portion of the duodenum of normal appearance. Concluding with a diagnosis of acute active chronic gastropathy of the body and antrum and 3 mm Paris-Isp gastric polyps, in addition to this, polypectomy is performed with biopsy forceps.The approach taken with this patient was based on hemodynamic stabilization with crystalloid solutions, without the need for vasopressor support, followed by transfusion of blood products with 3 globular packages, metabolic control by means of hypoglycemic agents and insulin, as well as compressive nasal packing, antibiotic coverage was administered to reduce the risk of toxic shock syndrome. The patient had a favorable evolution, leaving the hospital one week later, stable and without complications.

Discussion

While it is true that HHT is characterized by multiple arteriovenous malformations in different parts of the body characterized by a damaged endothelium with inflammation and abnormal angiogenesis, this condition can be potentiated by the vascular damage caused by SARS-CoV-2 infection. This is where

the importance of the association between these two pathologies lies, as was observed in the patient with Rendu-Osler-Weber syndrome, since throughout her life she had not presented severe hemorrhagic complications, but after suffering COVID-19, bleeding events increased, thus reaching the point of hypovolemic shock. As we know, COVID-19 is a multisystemic disease that can cause severe lesions in the organism, secondary to the binding of the ACE2 receptor which is mainly found in alveolar epithelial cells and even in small intestine enterocytes, however this receptor can be expressed in vascular endothelial cells, thus explaining the damage to this tissue, altering its correct functionality which translates into a higher risk of haemorrhages [26]. Due to the time of evolution in which the patient presented, taking into account the primo infection and her varied symptomatology, she meets the criteria for post-COVID-19 syndrome [27]. It is important to mention that the incidence among HHT within the context of SARS-CoV-2 infection does not appear to be lower than in the general population. Likewise, a study conducted at the Department of Molecular Biomedicine, Centro de Investigaciones Biológicas Margarita Salas, Madrid Spain, found that HHT patients infected with SARS- CoV-2 do not suffer a more severe infection than the general population, but on the contrary have a mild to moderate disease, which explains why our patient had a mild COVID-19 disease [28,29]. It has been described in the literature that COVID-19 can propitiate a process of angiogenesis by activating endothelial cells through tropism, production of chemokines and growth factors, thus leading to a proangiogenic environment mechanism called Intussusceptive Angiogenesis (IA) where there is vascular remodeling of redundant or ineffective blood vessels, secondary to extensive endothelitis and capillary microthrombosis observed in COVID-19.This process is regulated by Fibroblast Growth Factor (FGF2), which acts on the endothelium and pericytes through some receptors (tyrosine kinase) on the cell surface, which induces certain vascular permeability and vasodilatation forming intraluminal intussusceptive pillars, these mechanisms favor angiogenesis in this proinflammatory and hypoxic situation [30]. The probability of hemorrhage increases significantly due to the afore mentioned, not to mention that in COVID-19 there is a severe proinflammatory state (or so-called cytokine storm), which leads to an increase in the consumption of coagulation factors such as fibrinogen by indirect activation of these factors, it has also been described that there is a reduction in platelet count which results in an increased risk of thrombohemorrhagic events [25].

Therefore, based on these mechanisms, it could lead to a higher risk of epistaxis in these patients, as well as a higher incidence of gastrointestinal tract bleeding after SARS-CoV-2 infection; since HHT causes a process of unstable endothelial remodeling characterized by aberrant capillary vessels and on the other hand we have the angiogenic and hemorrhagic stimulus originated by the virus itself. If we associate these two pathologies, the clinical repercussions of this patient could be explained. However, more conclusive results that affirm and prove these theories are awaited [30].

Conclusion

Although Rendu-Osler-Weber disease is not a pathology with a high incidence, it deserves an important attention after contracting COVID-19, since these patients present an abnormal angiogenesis. In addition, if endothelial damage and the thrombohemorrhagic state induced by the inflammatory response mediated by the SARS-COV- 2 cytokine storm are added, may translate clinically into an increased risk of bleeding, which was the case of the patient, since the clinical manifestations of hemorrhage occurred within the post-COVID-19 syndrome period more frequently and in greater volume, with respect to her previous events, leading to hypovolemic shock and other repercussions of her own. However, this association is still not well investigated, which is where the importance of describing this phenomenon lies, so that in the near future, more research can be carried out to corroborate this theory and even transport it to some other vascular diseases, in order to establish prevention and early treatment.

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