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EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2023,18 (21) 99-102
(*FORMERLY: CAPSULA EBURNEA*)

Case Report

WERE SARS-COV-2 OR ACE-I RESPONSIBLE FOR ANGIOEDEMA OR WAS IT CAUSED BY A SECOND STRIKE? A CASE REPORT

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ARTICLE INFO

Article history:
Received 13 Jun 2023
Accepted 27 Aug 2023
Published 16 Sep 2023

Keywords:
Angioedema; SARS-CoV-2; ACE-Is; ACE-2; Chest HRCT.

ABSTRACT

Angioedema is characterized by swelling of the skin, mucosa, and submucosa, involving the deeper connective tissues. It can be triggered by allergic or non-allergic mechanisms, including the use of Angiotensin-Converting Enzyme Inhibitors (ACE-Is). SARS-CoV-2 has also been associated with angioedema, although the underlying mechanism remains poorly understood. This case report presents a middle-aged Caucasian woman who tested positive for SARS-CoV-2 and subsequently developed angioedema, along with impaired consciousness, acute respiratory acidosis, and severe respiratory distress requiring intensive care unit admission and mechanical ventilation. The patient had been on long-term ACE-Is for hypertension. High-resolution computed tomography revealed SARS-CoV-2 interstitial pneumonia. While the angioedema resolved within 48-72 hours, the patient's clinical improvement was attributed to the administration of corticosteroid therapy, anticoagulant drugs, and oxygen therapy, allowing for successful weaning from mechanical ventilation and resolution of respiratory failure and interstitial pneumonia. The exact cause of angioedema in this patient remains unclear, as it could be attributed to ACE-Is as a known side effect, SARS-CoV-2 infection as an unusual manifestation, or a potential interaction between the two. This case underscores the need for further research to elucidate the interplay between SARS-CoV-2 and ACE-Is in the context of angioedema development.

1. Introduction

Angioedema (AE) is a condition characterized by localized swelling of the skin, mucosa, and submucosa, which can affect various parts of the body, including the face, lips, throat, and genitalia. [1]AE is caused by a raising of the vascular permeability as result of allergic or non-allergic mechanisms. It can be categorized as either allergic AE (AAE) or non-allergic AE (NAAE), depending on the underlying mechanisms involved.

NAAE includes different forms, such as angioedema induced by Angiotensin-Converting Enzyme Inhibitors (ACE-Is), a class of antihypertensive medications. [2] The exact mechanisms by which ACE-Is modulate ACE-2 receptors levels are not fully understood, but it has been observed that approximately 0.1%-0.7% of patients taking ACE-Is can develop AE. [3,4]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta-coronavirus responsible for the global COVID-19 pandemic.

The SARS-CoV-2 pandemic has had a significant impact on epidemiology, leading to a notable global mortality rate. This impact has been particularly pronounced in certain countries within the Euro-Mediterranean region, often referred to as "high-income countries," such as Italy, Spain, and France. In this context, various environmental pollutants and climate-related factors like temperature, humidity, and seasonal variations have played a role in facilitating the transmission of SARS-CoV-2.

Furthermore, socio-demographic elements such as migration patterns and population density, as well as cultural dynamics like intergenerational social interactions between the youth and the elderly, have likely played a part in the circulation of the SARS-CoV-2 virus, alongside the healthcare infrastructure. [5]

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DOI: 10.3269/1970-5492.2023.18.21
 ISSN: 2279-7165 - Available on-line at www.embj.org

SARS-CoV-2 exhibits a high affinity for ACE-2 receptors, which are widely expressed in various organs and tissues, including the oral and nasal mucosa, nasopharynx, lungs, brain, kidney, endothelial cells, and gastrointestinal tract. [6]

ACE-2 receptors serve as the entry point for SARS-CoV-2 into human cells, facilitating infection. [7] Since AE is a side effect of ACE-Is and SARS-CoV-2 can modify ACE-2 levels, there is a potential interplay between these two factors in the development of AE. [4,6] In this case report, we present the case of a woman who was on ACE-Is for hypertension and tested positive for SARS-CoV-2, subsequently developing angioedema. We aim to explore the potential cause of angioedema in this patient and elucidate the possible interaction between SARS-CoV-2 and ACE-Is in its onset.

2. Case Presentation

A Caucasian woman in her mid-50s was admitted to the emergency room for worsening symptoms following 3 days of dysphonia, dysphagia, throat pain and neck swelling. SARS-CoV-2 infection was microbiologically confirmed by a positive SARS-CoV-2 nasopharyngeal molecular swab. Observations during the physical examination include: an increased respiratory rate (30 acts/min) with SpO2 92% on room air; rapid and shallow breathing using accessory respiratory muscles; at thoracic auscultation, respiratory crackles in lower right lobe were heard. Initially, a systemic corticosteroid therapy (Betamethasone 4 mg) and oxygen therapy (OT) via Venturi mask fraction of inhaled oxygen (FiO2) - 4L/min were administered. The medical history of this smoker (10 pack/year), fully vaccinated for SARS-CoV-2, was characterized by hypertension on ACE-I for years, hypothyroidism and obesity (body mass index: 31.22 kg/m²). Her personal anamnesis was negative for asthma and allergy. Three hours after the admission she had a sudden and severe worsening of her clinical conditions with the development of AE (Figure 1A-B), glottis swelling and impairment of consciousness.

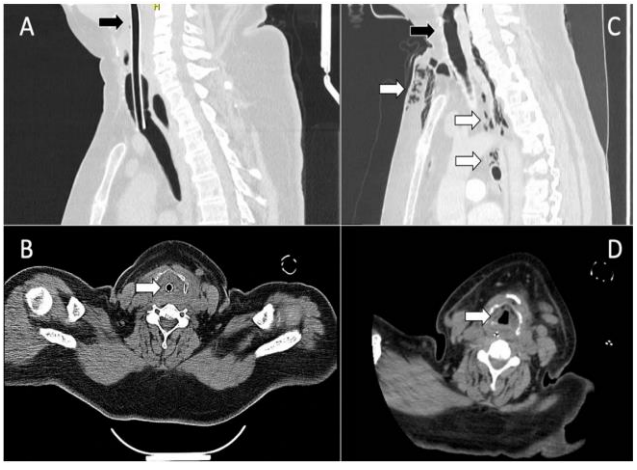

Figure 1. A-B: Neck and chest CT scans performed at day 0 show the angioedema and the endotracheal tube correctly placed (arrows); C-D: Neck and chest CT scans performed at day 10 highlight the resolution of the angioedema and an airways' caliber increase (Figure 1C, black arrow) (Figure 1D, arrow) and the development of subcutaneous emphysema and pneumomediastinum (Figure 1C, white arrows).

The arterial blood gas analysis (ABG) showed an acute respiratory acidosis (pH 7.0, pCO2 88 mmHg) which required a rapid intensive care unit (ICU) admission, where she received tracheostomy after a few hours for starting invasive mechanical ventilation (IMV) since endotracheal intubation (ETI) (Figure 1A-B) was partially successful.

At the admission, after systemic corticosteroid and OT, the very first ABG showed: pH 7.37, pCO2 37.6 mmHg, SatO2 96.1%, Lac 2.6 mmol/l, HCO3- 22.9 mmol/l. For evaluating SARS-CoV-2 interstitial pneumonia, a chest high resolution computed tomography (HRTC) was performed, which highlighted an involvement of lung interstitium described as ground glass opacities (GGOs) and parenchymal consolidations (Figure 2A-B).

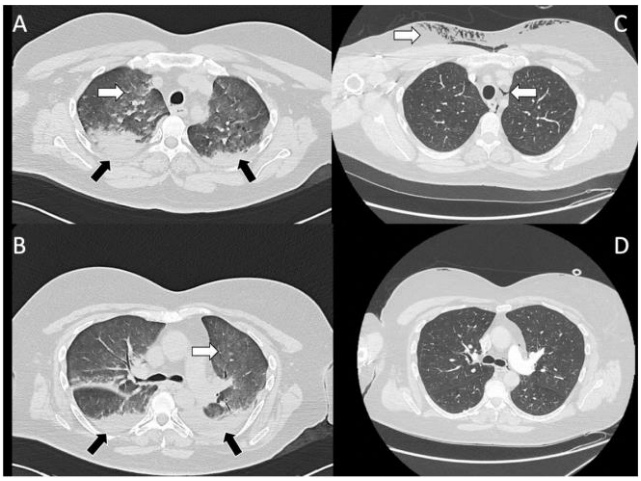

Figure 2. A-B: The chest HRTC at day 0 reveals GGOs (white arrows) and binasal parenchymal consolidations (black arrows); C-D: The chest HRCT at day 10 highlights the resolution of GGOs and parenchymal consolidations; pneumomediastinum is now evident (white arrows).

In ICU, the management of acute respiratory acidosis with IMV lead to the resolution of the respiratory acidosis. The biochemical markers highlighted an increased procalcitonin (PCT) (25.29 ng/L), D-Dimer (21293 ng/mL), fibrinogen (511 mg/dL) and C-reactive protein (CRP) (240.1 ng/L), a normal hemoglobin (129 g/L) and a rising white blood count (WBC) (12.32 x 10^9/L) with neutrophilia (10.50 x 10^9/L or 85.3%). Since WBC and PCT rising could be related to bacterial superinfection, microbiological tests were performed that turned out negative and a chest X-ray showing GGOs (Figure 3A) related to interstitial pneumonia. Several days after, the patient was re-evaluated with HRTC: neck scans displayed nasopharyngeal and hypopharyngeal edema; chest scans demonstrated, instead, GGOs, pneumomediastinum (Figure 1C) and parenchymal consolidations related to SARS-CoV-2 infection. Before moving into the pulmonology ward, in order to close tracheostomy, the patient underwent a video-laryngoscopy, which did not show any significant contraindication. At pulmonology ward admission, the full blood count cells showed WBC (12.48x10^9/L), neutrophil count (7.33x10^9/L) and lymphocytes count (4.39x10^9/L), hemoglobin (126 g/L) with a reduction of D-Dimer (4626 ng/mL) and Fibrinogen (411 mg/dL).

A few days later, for increasing D-Dimer (5036 ng/ml) an angio-CT was carried out which excluded pulmonary embolism. Fourteen days after the first positive COVID-19 nasal swab, she completed the viral clearance and turned negative, the last chest X-ray (Figure 3 B) improved, the respiratory failure was completely resolved and she was subsequently discharged at home on room air.

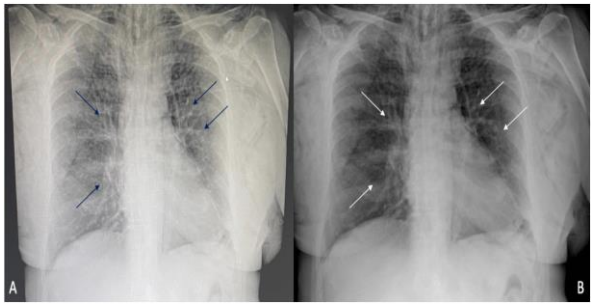

Figure 3. A: Chest X-Ray at day 2 shows a raise of radiopacity (arrows) related to the involvement of lung interstitium (GGOs); B: Chest X-ray at day 14 which highlighted the resolution of interstitial lung involvement (arrows).

The clinical presentation differs from the most common SARS-CoV-2 symptoms and signs. Dysphonia, dysphagia, throat pain and neck swallow are not specific manifestations, they could be related to many microorganisms, both bacteria and viruses, which have a strong tropism for upper airways, not only SARS-CoV-2. The further development of AE and glottis swelling was unexpected. We considered two major suspects as pathogenic causes: SARS-CoV-2 infection or the interaction between SARS-CoV-2 and patient's chronic hypertension treatment with ACE-Is.

While the management of angioedema was based on supportive care, and the consequent acute respiratory acidosis was managed with IMV, SARS-CoV-2 interstitial pneumonia was treated, following COVID-19 ERS guidelines, with the administration of systemic corticosteroid therapy (Dexamethasone 6mg/die for ten days), OT (both high-flow-nasal-cannula and conventional OT via Venturi mask when PaO2/FiO2 ratio raised over 200 mmHg) and anticoagulant therapy administering low molecular weight heparin (LMWH) 4000 UI/bis in die, switching to a single-use administration from the withdrawal of OT to patient's discharge. [8]

AE self-resolved in 48-72 hours (Figure 1C-D), acute respiratory acidosis has been corrected through IMV and respiratory failure resulting from SARS-CoV-2 interstitial pneumonia had a progressive improvement until resolution and was highlighted by ABG (Table 1). After mechanical ventilation weaning, the patient was put on HFNC OT (flow 60 L/min) with FiO2 60% in ICU and a few days later she was switched to conventional OT via Venturi mask FiO2 35%. We completely suspended OT when a PaO2/FiO2 >300 mmHg had been reached (Figure 4). The gradual improving of PaO2/FiO2 went hand in hand with the resolution of interstitial pneumonia at chest HRCT (Figure 2 C-D). SARS-CoV-2 swab resulted negative fourteen days after the first positive swab and the patient was discharged at home on room air.

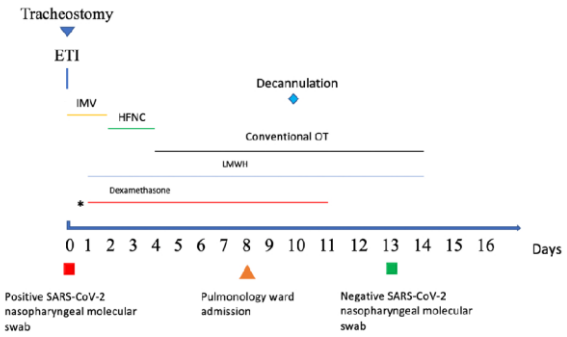

Figure 4. Hospitalization Summary: Throughout hospitalization the patient received ventilatory support and on day 0 (D0) she was intubated (ETI). After a few hours, she received tracheostomy and continued invasive mechanical ventilation (IMV) (yellow line) until D2, then she was put on HFNC OT (green line) until D4. Finally, she was on conventional OT (black line) until D14. In the meanwhile, tracheostomy was closed on D10 (blue rumble). During hospitalization, the patient was on systemic corticosteroid therapy (dexamethasone 6mg daily) from D1 to D11 (red line) and anticoagulant therapy (LMWH 4000 UI twice daily) (blue line). She was moved from the ICU to the pulmonology ward on day 8 (orange triangle). The red and the green square respectively represent the first positive SARS-CoV-2 molecular nasal swab and the negative one. She was discharged at home on day 16.

Fraction of inhaled oxygen (FiO2)	pH	pO2 (mmHg)	pCO2 (mmHg)	HCO3- (mmol/l)	PaO2/FiO2 ratio (mmHg)
21%	7.37	N/A	37.6	22.9	N/A
N/A	7.0	N/A	88	N/A	N/A
N/A	7.29	N/A	55	N/A	N/A
40%	7.39	104	40	24.2	260
30%	7.49	68	32	24.7	226
35%	7.44	75.1	39.7	27.3	215
28%	7.43	75.4	41.6	27.6	269
21%	7.42	67.2	40.7	26.1	320

Table 1. Arterial blood gas analysis (ABG) from admission to discharge

4. Discussion

AE is a severe and life-threatening disease characterized by different pathogenetic mechanisms. It can be distinguished into two main forms: allergic AE (AAE) and non-allergic AE (NAAE). AAE, also called "histaminergic angioedema", might be triggered by Immunonoglobulin-E (IgE) or may be non-IgE related. AAE non-IgE related is provoked by cysteine leukotrienes' pathway such as NAE with urticaria also known as "non-histaminergic angioedema" (NIA).

Likewise, NAAE or NIA with the absence of urticaria can be caused by bradykinin. NAAE also encompasses: hereditary and acquired AE, AE induced by ACE-Is or Angiotensin receptor blockers (ARBs) mediated by bradykinin, pseudoallergic AE triggered by leukotrienes and an isolated form called idiopathic AE. [1,2]

On the other hand, ACE-Is are a class of medications commonly used to treat conditions such as hypertension and heart failure. ACE-Is block the enzyme Angiotensin-Converting Enzyme (ACE), which normally converts Ang I to Ang II. By inhibiting ACE, ACE-Is can increase levels of bradykinin, as ACE is responsible for breaking down bradykinin.

This can lead to side effects such as AE, particularly in individuals who are predisposed to bradykinin-mediated AE. [9] Actually, although AE is a known side effect of ACE-Is and ARBs, ACE-Is and ARBs effects on ACE-2 are poorly known. There are different theories: some authors support that ACE-Is and ARBs seem not to modify the expression of ACE-2 levels, other authors proposed that ACE-Is and ARBs can modulate ACE-2 expression. [3,7] As of now, SARS-CoV-2, the virus accountable for the COVID-19 pandemic, continues to pose a substantial challenge. However, various therapeutic approaches within a hospital environment have been suggested. The utilization of systemic corticosteroids, oxygen therapy (OT), and anticoagulant treatment using LMWH (low-molecular-weight heparin) has gained approval for treating hospitalized patients with SARS-CoV-2. Furthermore, the antiviral medication Remdesivir has been incorporated as a viable treatment option for critically ill hospitalized patients. [10] SARS-CoV-2 enters cells by binding to the ACE-2 receptor, which is widely expressed in various tissues, including epithelial cells in the lungs. [6]

This binding can lead to downregulation of ACE-2 levels. [7] ACE-2 plays a role in the renin-angiotensin-aldosterone system (RAAS) and is involved in the conversion of angiotensin II (Ang II) to angiotensin-(1-7) [Ang-(1-7)]. Ang-(1-7) has vasorelaxant and anti-inflammatory properties. [7] Due to its protective activity, ACE-2 downregulation and Ang-(1-7) degradation could worsen SARS-CoV-2 infection gravity. Therefore, SARS-CoV-2 represents a trigger for AE's development since it binds ACE-2, widely expressed into epithelial lung cells and other tissues, determining ACE-2 down regulation.

The reduction of ACE-2 levels caused by SARS-CoV-2 infection may disrupt the balance of the RAAS, leading to an increase in bradykinin and substance P levels. Bradykinin is a potent inflammatory mediator and can induce vasodilation, while substance P is involved in the transmission of pain signals and inflammation. Increased levels of bradykinin and substance P can contribute to the development of AE. [11]

The question of whether ACE-Is can contribute to the development of AE in the context of SARS-CoV-2 infection is still uncertain and requires further investigation. Some theories propose that ACE-Is may increase the risk or severity of AE in individuals with SARS-CoV-2 infection due to their potential to further raise bradykinin levels.

However, the overall impact of ACE-Is on ACE-2 expression and their interaction with SARS-CoV-2 is not yet well understood.

5. Conclusions

The patient had been taking ACE-Is for a prolonged period and tolerated them well. The development of AE was likely influenced by the SARS-CoV-2 infection. The SARS-CoV-2 infection acted as a "second strike" that further increased the bradykinin levels, which were already altered due to ACE-Is.

The combination of SARS-CoV-2 infection and ACE-Is likely had a synergistic effect, leading to the development of AE.

Only a few similar cases have been described in the available literature. [3,12,13]

The role of ACE-Is in modulating ACE-2, a receptor involved in SARS-CoV-2 infection, is not well understood. Further studies are needed to investigate the relationship between ACE-Is, ACE-2 modulation, and the onset of AE, especially when a second strike, such as a viral infection, is present. These conclusions suggest that the interaction between ACE-Is and SARS-CoV-2 infection may have contributed to the development of adverse events in the patient. More research is required to understand the underlying mechanisms and the role of ACE-2 modulation.

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