ORIGINAL ARTICLE

MUC5AC gene expression in COVID-19 nasal discharge with rhinorrhea symptoms

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2. On May 1, 2021, there were 153 million confirmed positive cases worldwide with a total of 3.2 million deaths. The number of Indonesian cases on November 10, 2021, was recorded at 4,249,323 confirmed positive cases with 143,592 deaths. In COVID-19, rhinorrhea symptoms were found in 4% of cases, while in influenza and the common cold, 91% of cases experienced rhinorrhea. COVID-19 causes epithelial destruction and stimulates local immune response and the release of macrophages, monocytes, inflammatory cytokines, B cells, and T cells. The nasal epithelium is a physical barrier that protects the nasal mucosa from inflammatory agents by producing glycoproteins such as mucin, cytokines, and chemokines.

Materials and Methods: The study aimed to analyze the relationship between MUC5AC expression in nasal secretions and COVID-19 infection. This research was analytical research with a cross-sectional design. We used stored nasal swab samples at a laboratory designated for COVID-19 detection from 2021 until 2022, the pandemic. Selection of the sample using a simple random sampling technique. The population in this study were patients with a positive (n=40) and negative (n=40) diagnosis of COVID-19 confirmed by RT-qPCR and according to the inclusion and exclusion criteria. The data were analyzed using an independent Student's t-test.

Results: The sample characteristics in this study showed that 58% of females and 42% of males were confirmed positive for COVID-19. About 22% of COVID-19 positive cases had runny nose symptoms. The relative expression of MUC5AC increased 9.77 times.

Conclusion: MUC5AC expression is increased in the nasal secretions of COVID-19 patients, but this study found that only 22% of cases experienced symptoms of a runny nose.

KEYWORDS:
MUC5AC, runny nose, rhinorrhea, COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2. In December 2019 in Wuhan, China, there was an outbreak of pneumonia of unknown cause. Based on epidemiological data, WHO stated that until November 7, 2021, there were 294 million positive confirmed cases and more than 5 million deaths worldwide. In the United States, there were 510,968 cases, and in the United Kingdom, 252,104 cases. The Russian Federation reported a 3% increase in cases at 281,305 new cases. Turkey reported an 8% increase in new cases and Germany 29%. On May 1, 2021, there were 153 million confirmed positive cases worldwide with a total of 3.2 million deaths. (WHO. The number of Indonesian cases on November 10, 2021, was recorded at 4,249,323 confirmed positive cases with 143,592 deaths.[1]

COVID-19 causes epithelial destruction and stimulates local immune response and the release of macrophages, monocytes, inflammatory cytokines, B cells, and T cells. SARS-CoV-2 is a cytopathic virus, which causes cell damage and death. Viral infection and replication occur in the epithelium of the respiratory tract, causing pyroptosis followed by vascular leakage. Pyroptosis is an inflammatory process that is a cell death program often found in cytopathic viruses. The result of pyroptosis will stimulate the release of inflammatory cytokines.[2]

COVID-19 stimulates type 1 immune responses and the release of pro-inflammatory cytokines. Several studies have mentioned that in COVID-19 there is an increase in IL-1ß, which induces the production of MUC5AC mucin in the respiratory tract. IL-1ß induces MUC5AC production through regulation of cAMP response element-binding protein (CREB)-dependent NF-kB transcription. The COVID-19 inflammatory response causes mast cell dysfunction. Mast cells stimulate the synthesis of TNF-α, which can be released rapidly. The release of COVID-19 histamine causes inflammation, platelet aggregation, bronchial constriction, vasodilation, edema, and mucus secretion.[3]

There are 22 types of mucin genes expressed in the human airway epithelium. MUC5AC and MUC5B are mucins that function to maintain nasal epithelial hemostasis. The main components that make up mucin are glycoproteins encoded by several mucin genes. The MUC5AC gene is produced by epithelial goblet cells, while MUC5B is produced by submucosal glandulars in the lower airway.[4–6] The MUC5B genes are predominantly found in normal conditions, which function to keep the epithelium in a normal state by

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controlling bacterial infection and preventing further inflammation. In normal conditions, MUC5AC levels are found to be low. When a viral infection occurs, MUC5AC secretion will increase. MUC5AC acts as a decoy for viral receptors and is essential for the inflammatory response.[7]

Inflammation stimulates the release of inflammatory mediators such as TNFα, IL-9, IL-4, acrolein, neutrophilelastase, oxidative stress, and Epidermal Growth Factor Receptor (EGFR), which will induce an increase in MUC5AC production.[8,9] Ali et al. found 75% MUC5AC increased in nasal polyps.[10]

Mucin functions as a protective barrier and intercellular signal transducer that has a role in maintaining homeostasis and survival in epithelial cells. In advanced infections, mucin expression can become pathological. Mucin hypersecretion is the main clinical symptom seen in COVID-19, and it has severe symptoms. The accumulation of mucus in the respiratory tract causes airflow obstruction, making it difficult for patients to breathe and worsening the course of the disease.[11] COVID-19 stimulates the release and activation of an inflammatory cascade of cytokines and inflammatory chemokines that influence the inflammatory response and increase mucus secretion in the respiratory tract.[12]

In COVID-19, rhinorrhea symptoms were found in 4% of cases, while in influenza and the common cold, 91% of cases experienced rhinorrhea.[13] In other studies, rhinorrhea was found in only 4% of cases, and cough was still a common symptom.[14] Lovato, in his study, found symptoms of nasal congestion in COVID-19 in 3.7% of cases, while rhinorrhea was rarely found.[15]

MATERIALS AND METHODS

Experimental Design

This study protocol was approved by the Ethical Review Committee Faculty of Medicine, Universitas Andalas, Indonesia (613/UN.16.2/KEP-FK/2023). This research is analytical research using a cross-sectional design.

Sample Isolation

The research was conducted at the Laboratory of the Center for Diagnostics and Research of Infectious Diseases (PDRPI), Faculty of Medicine, Andalas University during 2021 until 2022, the pandemic. The samples in this study are biological materials stored in the Laboratory of the Center for Diagnostics and Research of Infectious Diseases (PDRPI), Faculty of Medicine, Andalas University. The sample population of this study was patients aged 20 to 40 years who were confirmed positive and negative for COVID-19 through RT-qPCR examination (using the Kaira-2019 nCov Detection KitTM). Control samples consisted of patients presenting with symptoms of viral rhinitis who underwent COVID-19 screening due to a history of contact with confirmed COVID-19 cases. All control subjects tested negative by RT-PCR.

RT-PCR analysis

RNA isolation from nasal discharge was conducted using the Kaira-2019 nCov Detection KitTM reagent. The IL-4, IFN-γ, and MUC5AC levels were measured by RT-PCR using specific primers and probes for the IL-4, IFN-γ, and MUC5AC genes. For relative quantification of the expression of the IL-4, IFN-γ, and MUC5AC mRNA, we used beta-actin primers.

The IL-4 *was used with primer sequences as follows:* 5'TTGGCTTAATTCTCTCGG'3, and the reverse primer sequence was used 5'TTTACATATGGGTCCTGG3'. The IFN-γ *was used with primer sequences as follows:* 5' TGGGTTTTACTTAGCTTTGG'3 and the reverse primer sequence was used, 5' GGCGATACCTTTTCTGTT'3. The MUC5AC γ *was used with primer sequences as follows:* 5' CTCCTACCAATGCTCTGTA'3 and the reverse primer sequence was used 5' GTTGCAGAAGCAGGTTTG'3. The *beta-actin primer was used as a control with the primer sequences as follows:* 5'CATGTACGTTGCTATCCA'3, and the reverse primer sequence was used 5' TTCATGAGGTAGTCAGTC'3.

Data analysis

Data were analyzed by SPS. The normality of IL-4, IFN-γ, and MUC5AC gene expression data in nasal discharge, runny nose, and anosmia in COVID-19 patients was tested. The data was analyzed by means of an independent T-test.

RESULTS

Characteristic of sample

Based on Table I, the demographic distribution of the sample based on gender in the control population is 60% female and 40% male. In the case population, 58% of the samples were female and 42% male. There were clinical symptoms of COVID-19 found in the case population, namely runny nose in 22% of cases, anosmia in 18% of cases, and nasal congestion in 25%. There were no symptoms of anosmia in patients with confirmed negative COVID-19.

Based on the symptoms of a runny nose with the expression of IL-4, IFN-γ, and MUC5AC in the nasal secretions of COVID-19 patients, the largest standard deviation value is obtained in IFN-γ with runny nose symptoms, namely 2.08 with an average value of 19.8, a minimum value of 16.54, and a maximum value of 22.64. The smallest standard deviation was obtained in the MUC5AC group with non-runny nose complaints, namely 0.86 with an average of 9.78, a minimum value of 8.28, and a maximum value of 11.42. Expression of IL-4, IFN-γ, and MUC5AC Expression with Runny Nose

The relative increase in IL-4 expression in COVID-19 with runny nose symptoms (Figure 2) is 4.75 times higher than in COVID-19 without a non-runny nose. IFN-γ expression in COVID-19 with runny nose symptoms also increased 1.58 times higher than in COVID-19 without runny nose. MUC5AC gene expression in COVID-19 with a runny nose has increased 9.77 times higher compared to COVID-19 without a runny nose.

DISCUSSION

Rhinorrhea, or runny nose, is a symptom that often occurs in COVID-19. In this study, 22% of patients had a runny nose, 18% had anosmia, and 75% had nasal congestion. El Anwar, Esa M et al. found as many as 20% of patients experienced a

runny nose.[16] Khongsiri et al. found that in the Omicron variant, 40.2% of cases had a runny nose. Omicron variants have a tendency to infect the upper airway. So that in the wave of omicron variants, the dominant symptom that appears is a runny nose or nasal congestion.[17]

A runny nose and sneezing are the body's protective mechanisms when infected by a virus. Mucus produced by the epithelial mucosa functions as a mucoprotector. T. Klopfenstein et al. found that 57% of runny nose symptoms were followed by nasal obstruction. More than 85% of anosmia cases are followed by dysgeusia.[18] Lechien et al. found that 66.2% had anosmia and 13.5% had hyposmia.[19] The physiology of smell involves a complex process of interaction of olfactory compounds with chemoreceptors involving olfactory neurons and airflow conduction. Olfactory disorders can be caused by sensorineural damage or damage to airflow conduction.

COVID-19 is a new viral infection. Researchers assume that perhaps at the beginning of infection, the body's immunity has difficulty recognizing this virus, so this virus tends not to be detected at the beginning of infection. In the first mechanism, SARS-CoV-2 on the ciliary surface will bind to ACE2 through the receptor binding domain (RBD) and then activate through proteolysis. oleh TMPRSS2, which will activate protein S, and then fusion occurs on the ciliary membrane. In the second mechanism, the SARS-CoV-2-ACE2 complex will be transported from the tip of the cilia to the cell body to the cell membrane, and then fusion occurs through the process of endocytosis. This mechanism causes COVID-19 infection to go unrecognized at first. Ahn et al. found SARS-CoV-2 damaged the mucociliary system in the nose. Ahn found that there was an increase in ACE2 receptor levels in the apical cells of the nasal epithelium, the expression of ACE2, TMPRSS2, and FURIN protein on goblet cells in the nasal epithelium, while the MUC5AC gene was rarely found or found in low expression; this is in accordance with the findings of the low percentage of rhinorrhea symptoms in COVID-19 patients.[20]

To prevent pathogen infection, the epithelium increases mucus expression. MUC5AC is the dominant mucus secreted to fight pathogens. Morison et al. found that the rapid spread of SARS-CoV-2 infection caused goblet cells to fail to secrete mucus. Intracellular MUC5AC is depleted.[21] Lu et al. reported an increase in MUC5AC levels in COVID-19. The retention of mucus in the respiratory tract causes hypoxia, and patients require bronchoscopic aspiration.[22] Kumar et al. reported an increase in MUC2, MUC5AC, and MUC5B in COVID-19. In this study, it was found COVID-19 stimulates IFN-γ and IFN-β to activate aryl hydrocarbon receptor signaling (Ahr) and stimulate the formation of mucin genes.[23]

This study found that the expression of MUC5AC in COVID-19 increased by 9.77 times. The resulting reactive oxygen species and inflammatory mediators cause mucus gene expression to increase. Mucus works to reduce viral load. Lee et al., in nasal mucosal epithelial cultures, found that MUC5AC expression increased due to the spike protein RBD SARS-CoV-2.[24] In this research, there is a significant relationship between the expression of IL-4 and IFN-γ in COVID-19 with a runny nose. The IL-4 expression and COVID-19 with a runny nose increased 4.75 times. Wang et al. cultured MUC5AC goblet cells and transient secretory cells. Wang found that goblet cells and transient secretory cells are vulnerable to COVID-19.[25]

The pro-inflammatory cascade not only disrupts mucus secretion but also impairs cilia function. Therefore, this condition can trigger recurrent infections and lead to airway obstruction. Damage to the mucociliary system leads to obstruction or congestion of the nose. Excessive mucus production causes nasal congestion. COVID-19 disrupts respiratory epithelial cell homeostasis by increasing excess mucus production, resulting in respiratory obstruction.21 The inflammatory response releases a pro-inflammatory cascade that not only disrupts mucus secretion but also disrupts cilia function. Therefore, this condition can trigger recurrent infections in the airway and cause more obstruction. [12]

The IL-4 expression in COVID-19 with runny nose symptoms was found to be 4.75 times higher. Yin et al. found MUC5AC increased in COVID-19 infection. There was hyperplasia of goblet cells, hypoplasia of club cells, and also multiciliated cells. COVID-19 disrupts respiratory epithelial cell homeostasis by increasing mucus production, which can lead to obstruction.[21] The inflammatory response in the form of the release of pro-inflammatory cascades not only disrupts mucus secretion but also disrupts cilia function. Therefore, this condition can trigger recurrent infections in the airway and cause more obstruction.[12]

Proinflammatory and anti-inflammatory processes occur together in the body. This balance is important for maintaining homeostasis and responding to various invasions. When an infection occurs, immune cells trigger a proinflammatory response to fight the pathogen. Simultaneously, anti-inflammatory mechanisms work to suppress the inflammatory process and prevent excessive damage to healthy tissues. This interaction ensures a controlled and effective immune response. Viral or toxin infections cause an inflammatory response in the form of immune cell infiltration and cytokine production. Inflammation induces olfactory-sensitive neuron degeneration and apoptosis as a protective mechanism.[26]

The infection process due to coronavirus will be responded to by the immune system, producing several cytokines, including IL-4 and IFN-γ. The IL-4 plays a role in the activation of B cells in antibody production and the production of several types of cytokines. The IFN-γ, as a type 1 interferon, plays a role in proinflammation by helping activate macrophages to become M1 and increasing antigen presentation, thus triggering an immune response against infected cells. IFN-γ can also play an anti-inflammatory role. The IFN-γ activation contributes to the activation of macrophages to M2, helping the resolution of the infection process and promoting tissue repair, indirectly affecting the anti-inflammatory process. Low IFN-γ response at the beginning of infection will lead to increased viral load and progressive inflammation due to local immune dysfunction.[26] The involvement of IL-4 and MUC5AC in the infection process due to COVID-19 is through a complex

immunological process. Excessive immune response can result in inflammation and mucin production that contributes to respiratory symptoms.[27]

This study has several limitations. First, to find out the patient's symptoms, one must be on the phone, so there is a time interval between the examination and the symptoms felt so that we cannot know directly the condition of the patient. Second, this study does not differentiate between COVID-19 virus variants. Researchers did not distinguish between acute and recovery phases when sampling.

CONCLUSION

There was an increase in the relative expression of MUC5AC in COVID-19 with runny nose symptoms.

ETHICS APPROVAL

This study protocol was approved by the Universitas Andalas Ethics Committee (Ethical Code: 613/UN.16.2/KEP-FK/2023) on December 13th, 2023.

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