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CASE REPORT

A COVID-19 Case: Isolated and Persistent Headache

Çiğdem Yalçın[1*] and Ali Kutta Çelik[1]

[1]*Mersin City Training and Research Hospital, Mersin, Turkiye*

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Abstract: COVID-19 effects many systems such as respiratory, nervous, renal and hematologic system. Third of patients have experienced neurological symptoms such as headache, anosmia, ageusia and dizziness. Headache has been reported as the most common neurological manifestation but cases just headache are extremely rare. This case is a Covid-19 case with no symptoms other than sudden onset headache. The result of the nasal swab PCR sampling was negative however local infiltration areas with ground glass density in the periphery of the middle lobe, lateral segment of the both lungs were detected in the thorax CT.

Keywords: Covid-19, headache**,** pain, infection.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and declared as a pandemic by the World Health Organization on March 11th 2020. COVID-19 effects many systems such as respiratory, nervous, renal and hematologic system. In severe disease, patients experience respiratory failure, acute renal failure, and ultimately multisystem organ failure.

COVID-19 is characterized by fever, cough, dyspnea, sore throat, myalgia, fatigue, diarrhea [1] and over a third of patients (36,4%) have experienced neurological symptoms such as headache, anosmia, ageusia and dizziness. Headache is the most common neurological manifestation [2]. The onset of headache associated with COVID-19 is typically within 24 hours of infection and lasts an average of 7 days. However, 13 percent of patients may develop persistent headaches lasting more than 1 month [3]. In a study by Caronna *et al.*, they reported that headaches continued 6 weeks after admission in 28 of 74 COVID-19 patients. The headache is usually bilateral, long lasting, and likely to be analgesic resistant [4].

Toptan *et al.* reported an isolated COVID-19 headache series consisting of 13 patients. In these some cases other symptoms appeared within 2-3 days following the diagnosis, such as diarrhea. Unlike our case, all of these patients were PCR positive and none of them developed persistent headache. In 70% of the cases, the headache ended within 3 days [5]. Asif et al reported a case with isolated headache in COVID-19, but in this case the cause of headache was sinus vein thrombosis [6]. In our patient, headache was the only symptom of COVID-19 and was persistent. Also in our case, asymptomatic pneumonia was present at the time of diagnosis, there were no other symptoms were observed during the treatment course. Our case is the only reported case with no other symptoms, but headache with pneumonia in thorax CT.

**Correspondence should be addressed to Çiğdem Yalçın, Mersin City Training and Research Hospital, Mersin, Turkiye. Email: mdcigdem@gmail.com.tr*

2. CASE REPORT

56-years-old female patient initially admitted to the emergency department with complaint of a sudden headache. The pain started from the neck and spread to the entire head. The characteristic of the pain was throbbing on the first day. The next day it turned to a feeling of pressure in the head. The initial pain was very severe, sharp and different from the headaches she has experienced before. There was no accompanying nausea, photophobia, phonophobia, osmophobia, tearing-redness of the eyes, runny nose, fever, cough, sore throat, dyspnea, diarrhea, musculoskeletal pain, chest pain, anosmia and ageusia. The neurological examination was normal. There was no response to paracetamol, but a small relief with the non-steroidal antiinflamatuar drugs (NSAIDs).

The patient did not have any comorbidities and no previous diagnosis of migraine or any other headache syndrome. On the first day, cranial computed tomography (CT) and cranial CT angiography, cervical CT angiography and brain diffusion MRI were performed in the emergency department and reported to be normal.

Blood analysis revealed fibrinogen: 691,67 (180-350mg/dL), D-dimer: 0,97 (<0,55 mg/L), WBC:14,0 (4,5-11*10^3/uL), Neutrophils:11.1 (2-8 10^3/uL), CRP:3,84 (0-0,8 mg/dl), LDH:258 (120-246 U/L). The result of the nasal swab PCR sampling was negative. To rule out COVID-19, a chest CT was performed despite the absence of symptoms. However local infiltration areas with ground glass density in the periphery of the middle lobe, lateral segment of the both lungs were detected in the thorax CT (Figs. **1** and **2**). Bacterial pneumonia was ruled out as the procalcitonin level was normal and the patient was quarantined at home with the suspicion of COVID-19 pneumonia.

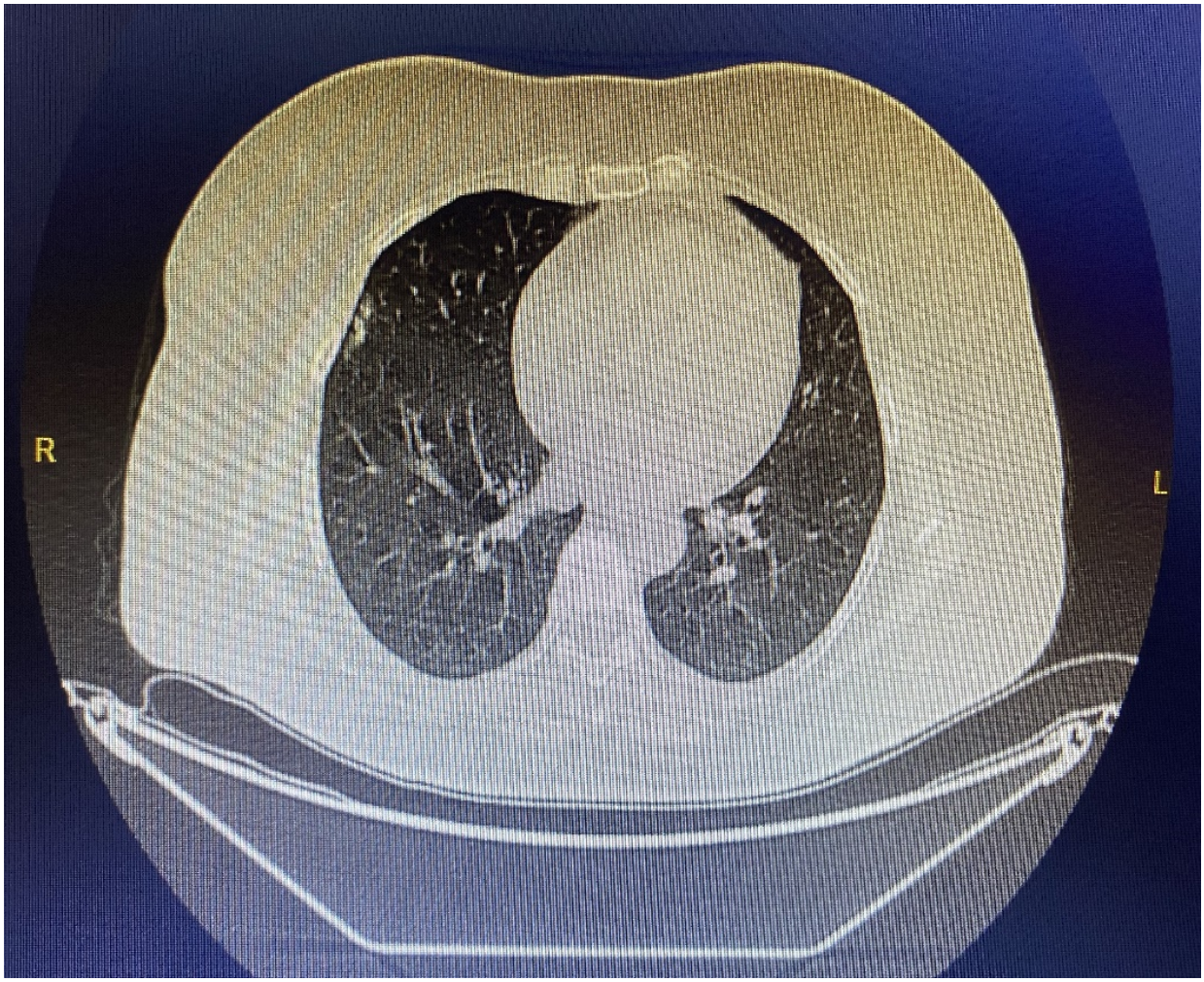

Fig. (1). Thorax CT: Small infiltrative area in middle lobe lateral segment.

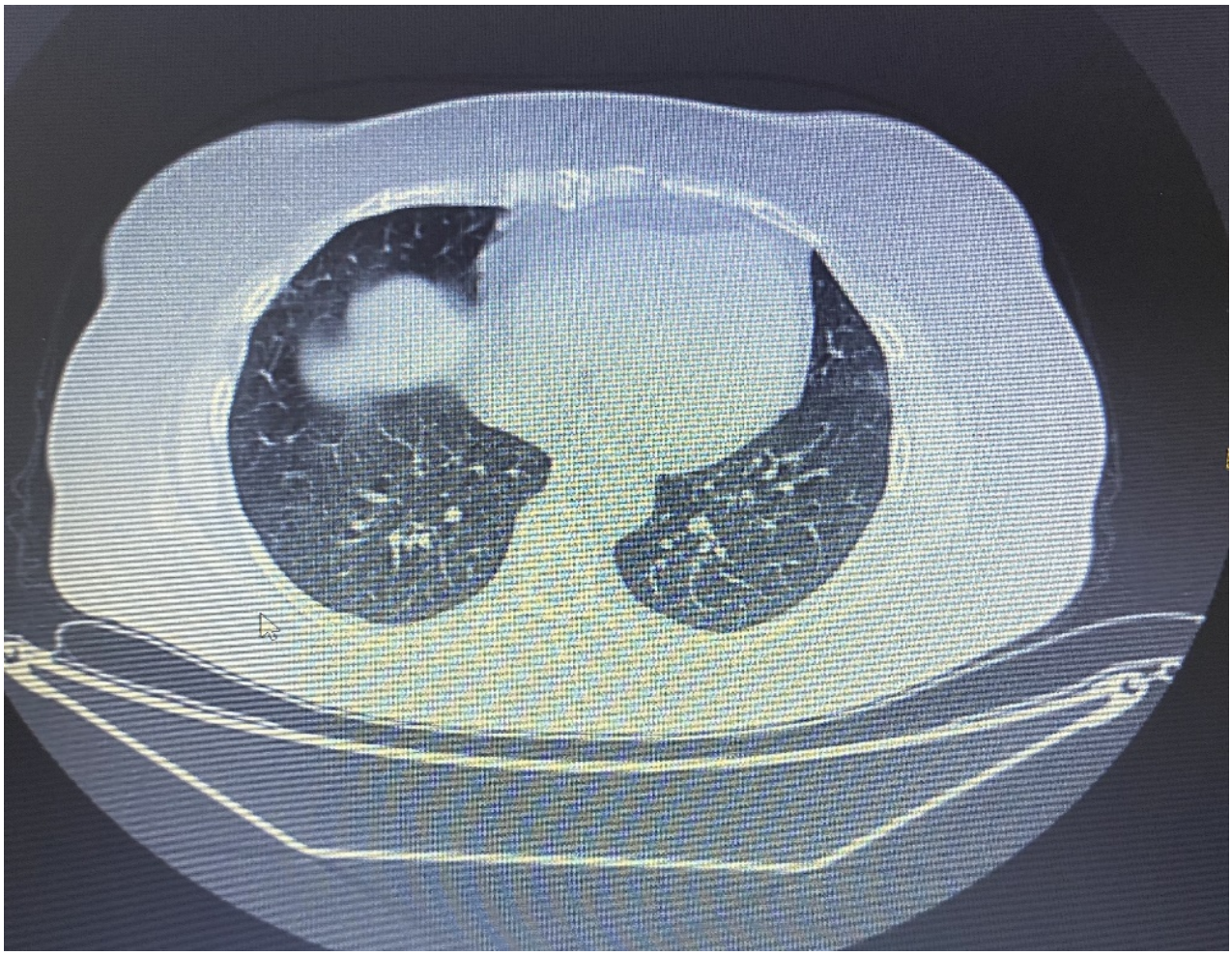

Fig. (2). Local infitration areas of both lung.

She was prescribed Hydroxychloroquine 200 mg tb oral every 12 hours for 5 days, Favipiravir 1600 mg oral every 12 hours on the first day, then 600 mg every 12 hours for the next 4 days, Famotidine 40 mg every 12 hours, Enoxaparin 6000 IU subcutaneously once a day. For her headache, she was prescribed Paracetamol 500 mg every 8 hours. On second day visit at home her complaints were still continuing, so paracetamol was replaced with Tramadol 100 mg every 8 hours for the first 7 days, then it was continued 50 mg every 8 hours for the following 3 days. The patient was followed up by phone calls to evaluate headache and other COVID-19 symptoms. She did not develop additional symptoms and the severity of the headache decreased approximately in 7 days. Therefore, additional tests and imaging were not performed. Mild persistent headache remained for about 2 months with paracetamol 500 mg three times in a day.

3. DISCUSSION

The pathophysiological mechanism of COVID-19-associated headache is still unclear. However, activation of trigeminal nerve endings, overproduction of pro-inflammatory cytokines, hypercoagulation, and hypoxia have been suggested as possible mechanisms [7]. SARS-CoV-2 uses the transmembrane angiotensin-converting enzyme type 2 (ACE2) receptor to enter mammalian cells. The ACE2 receptor is found on a variety of cells in humans, including lung epithelial cells, vascular endothelium, pericytes and smooth muscle cells, neuronal cells in the trigeminal ganglion, olfactory bulb, and other cortical and subcortical areas. Viral neuroinvasion is suggested to occur *via* synaptic transmission from infected cells, penetration into the brain *via* the olfactory groove, or perivascular lymphocytic infiltration [8].

There is evidence of a prolonged proinflammatory response (cytokine storm) in COVID19 patients, which can lead to rapid hyperactivation of T cells, macrophages, and natural killer cells and overproduction of more than 150 inflammatory mediators [9]. The cytokine storm triggers an atypical response of mast cells, a dramatic increase in interleukin-6 (IL-6) levels, and overexpression of angiotensin-converting enzyme 2 (ACE2) in the central and peripheral nervous systems [10, 11]. The same mechanisms play a role in migraine and tension-type headache. It is possible that this cytokine storm leads to hyperexcitability of the trigeminovascular system and triggers headache.

Molina-Gil *et al.* reported that only trigeminal neuralgia developed as a neurological symptom in a COVID-19 case. In this patient, as in our case, the PCR test was negative, but the rapid test showed positive IgM and IgG serologies for SARS-CoV-2. Again, as in our patient, an increase in D dimer was observed in this patient. Unfortunately, we could not perform a rapid test because it was not available in our hospital at that time [12].

At the beginning of the epidemic, due to Covid-19's similarities to SARS-CoV, many researchers recommended the use of hydroxychloroquine and chloroquine on the new virus [13,14,15]. At the same time, Wang and colleagues tested the effects of various Food and Drug Administration-approved antiviral drugs on the virus *in vitro*. In these studies, Chloroquine showed efficacy at the entry and post-entry level, whereas remdesivir was effective only at the post-entry level [16]. Yao and colleagues also tested the effect of hydroxychloroquine and chloroquine *in vitro* [17]. They found that hydroxychloroquine was more effective than chloroquine *in vitro* for both prophylaxis and treatment. As a result of these studies, hydroxychloroquine became one of the first agents used at the beginning of the COVID-19 epidemic. We believe that by using hydroxychloroquine in our patient, we benefited from the anti-inflammatory effect of the drug.

The International Classification of Headache Disorders third edition (ICHD-3) lists "Headache attributed to systemic viral infection" [18]. COVID-19 is clearly associated with headache and the character of COVID-19 headache was defined in a study [19]. This study included 130 adult patients. 97 patients had experienced headache as a COVID-19 symptom (74.6%). 19.6% patients had a history of episodic migraine and no patient had a history of chronic migraine. 37 patients had holocranial pain and the quality of pain was pressing and throbbing (68 and 19 patients, respectively). Nausea and vomiting (25,77%), worsening with movement (12,37%), photo/phonophobia (10,3%), vertigo (4,12%) and subjective neck stiffness (3,09%) were reported by the patients. 24 out of 97 patients had severe headache, 73 had mild-moderate pain, specifically analyzing migraine-like features. 74 of the patients with headache could be contacted after 6 weeks, 37.8% (28/74) still had headache. In our patient, headache was in the form of throbbing and pressure sensation and lasted more than 8 weeks.

There is a case with headache lasting more than 85 days reported in the literature [20]. The patient had been using naproxen and sumatriptan for the treatment of headache attacks. NSAIDs are not recommended as first choice for managing of COVID-19 disease [21]. Long term use of NSAIDs have been associated with higher rates of myocardial infarction, heart failure and stroke [22]. Acute respiratory tract infections are also associated with increased risk of myocardial infarction and stroke and short term use of NSAIDs during the illness is associated with further increases in risk [23]. The WHO declared to press that there is no evidence of an increased risk of death with the use of NSAIDs in COVID-19. Even so, we did not prefer to use NSAIDs for our patient. If paracetamol is inadequate, tramadol can be the second choice.

According to WHO, COVID-19 disease diagnosis is achieved with clinical manifestations, thorax CT and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). Our patient is included in the CT positive group [24,25,26]. In addition according to Pakdemirli and collegues, lung parenchymal changes due to COVID-19 can be clearly seen on chest CT, despite repeated RT-PCR negative results [27]. They described five patients with typical COVID-19 findings on CT scan despite two negative RT-PCR results. Also Brogna and collegues reported three cases, in which a chest CT was performed, showing lung changes characteristic of COVID-19 with multiple negative RT-PCR tests and positive serology for SARS-CoV-2 [28].

In a study, 87 patients underwent both CT scan and rRT-PCR to diagnose COVID-19 disease. 36 patients were diagnosed with COVID-19 pneumonia. The distribution of the CT lesions were 72,2% peripheral and 27,8% central. Peripheral distribution was more common than central distribution. According to this study, the sensitivity of CT was found to be 97,2% and the sensitivity of rRT-PCR was 83,3%. This may be related to collection of the samples at upper respiratory tracts. Additionally, the sensitivity of the rRT-PCR kit can also contribute to false negatives [29].

Higher or lower blood leukocyte count, higher neutrophil count and percentage, lower lymphocyte count and percentage, lower platelet count, higher C-reactive protein level, higher D-dimer level, higher alanine aminotransferase and aspartate aminotransferase activity, higher α - hydroxybutyrate dehydrogenase activity, higher lactate dehydrogenase activity and higher creatine kinase activity were related to severe 2019 novel coronavirus pneumonia [30].

In our case bilateral peripheral ground-glass opacity was defined in the thorax CT imaging. This was compatible with COVID-19. Additionally our patient's laboratory results were compatible with COVID-19. However rRT-PCR testing was negative. The negative result with pharyngeal or nasal swab technique in patients with pneumonia can be repeated by taking samples from the lower respiratory tract. Unfortunately, we did not make a second PCR sample in our patient.

CONCLUSION

In conclusion, the pathophysiology of COVID-19-associated headaches remains unclear, with some authors proposing direct viral invasion of the central nervous system *via* ACE2 receptors and retrograde spread through trigeminal nerve terminals, while others suggest an indirect mechanism involving activation of the trigeminal-vascular system due to a cytokine storm and elevated systemic inflammatory markers like calcitonin gene-related peptide. Given these varying hypotheses, further research is required to elucidate these controversial aspects. Clinicians should consider COVID-19 infection in patients with sudden onset of severe headaches, even in the absence of other symptoms, and pursue diagnostic evaluation with PCR testing and lung CT, particularly when cranial CT and CT-angiography results are normal.

AUTHORS' CONTRIBUTIONS

All authors contributed the study.

CONSENT FOR PUBLICATION

Written consent was obtained from the patient that the procedures to be carried out were photographed, including the appropriate parts of the body for medical, scientific, research or educational purposes, and that he accepted the record, provided that his identity is not disclosed in the images or in the article.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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