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Prikaz slučaja /
Case report

DIFFUSE COVID-19-ASSOCIATED LEUKOENCEPHALOPATHY WITH MICROHEMORRHAGES – *OUR EXPERIENCE*

DIFUZNA LEUKOENCEFALOPATIJA SA MIKROHEMORAGIJAMA POVEZANA SA COVID-19 – *NAŠE ISKUSTVO*

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Abstract

Introduction: Neurological complications related to SARS-CoV-2 are increasingly recognized. In diffuse leukoencephalopathy with microhemorrhages, non-contrast computed tomography (CT) can initially demonstrate extensive, fairly symmetrical hypodense areas in the supratentorial white matter and corpus callosum, while magnetic resonance imaging (MRI) shows diffuse, confluent hyperintensities, scattered microhemorrhages predominantly in subcortical WM and the corpus callosum without diffusion restriction or abnormal enhancement**. Case report:** Initial imaging evaluation with non-contrast CT of the brain revealed multifocal non-hemorrhagic white matter lesions in both cerebral hemispheres and cerebellum. A contrast-enhanced brain MRI showed non-enhanced diffuse, bilateral, symmetric, confluent hyperintensities located in the deep and subcortical white matter with the involvement of the frontal, parietal, temporal and occipital lobes, as well as the brain stem, bilateral capsula interna and cerebellum, suggesting vasogenic edema. A microhemorrhage was found in corpus callosum, posterior limb of capsula interne of the left and basal ganglia on the right side. MRI showed non-diffusion restriction. The thalami showed no alterations. MRI angiogram and venogram of the brain were unremarkable. A definitive diagnosis of COVID-19-related diffuse leukoencephalopathy with callosal microhemorrhages has been made, given the rapid clinical deterioration, progression of imaging characteristics, and CSF imaging. **Conclusion:** Diffuse leukoencephalopathy with microhemorrhages is rare and often fatal neurological complication of COVID-19. Heightened clinical awareness and early imaging identification of diffuse leukoencephalopathy with microhemorrhages can provide clinicians with the opportunity to pursue more aggressive treatment options, thereby reducing fatal outcomes.

Key words
COVID-19; leukoencefalopatija; mikrohemoragije

Ključne reči
COVID-19; leukoencephalopathy; microhemorrhages

INTRODUCTION

Neurological complications related to SARS-CoV-2 are increasingly recognized. The most frequent neurological complications of COVID-19 are encephalopathy, meningoencephalitis, stroke, seizures, Guillain-Barré syndrome and acute disseminated encephalomyelitis (ADEM) [1-4].

In diffuse leukoencephalopathy with microhemorrhages, non-contrast computed tomography (CT) can initially demonstrate extensive, fairly symmetrical hypodense areas in the supratentorial white matter and corpus callosum, while magnetic resonance imaging (MRI) shows diffuse, confluent hyperintensities, scattered microhemorrhages pre-

dominantly in subcortical WM and the corpus callosum without diffusion restriction or abnormal enhancement [2].

The aim of this manuscript was shown one case of patients with diffuse COVID-19-associated leukoencephalopathy with microhemorrhages.

CASE PRESENTATION

A 48-year-old previously healthy male was admitted to the emergency department due to fever, non-productive cough, and rapidly progressive dyspnea. PCR analysis of nasopharyngeal swab specimens confirmed the diagnosis of COVID-19. Chest radiograph showed bilateral peripheral zone consolidation.

Because of severe hypoxia, the patient received invasive mechanical ventilation (IMV) and was transferred to the intensive care unit (ICU). Relevant laboratory investigations on admission showed an increase in white blood cell count with high neutrophils and low lymphocytes; C-reactive protein of 30.2 mg/L (normal range 0–5 mg/L), with levels raising to more than 158 mg/L on the tenth day, and D-dimer of 0.26 mg/dL (normal range: 0–0.5 mg/dL), with levels raising to more than 2.5 mg/dL on the eighth day, which prompted the use of full anticoagulant therapy. High axial resolution pulmonary CT scan showed the pulmonary parenchyma with diffuse multiple ground-glass opacities with bilateral central and peripheral multilobar distribution together with the dominant consolidation of posterior segments. More then >90% of the parenchyma is affected (Fig. 1).

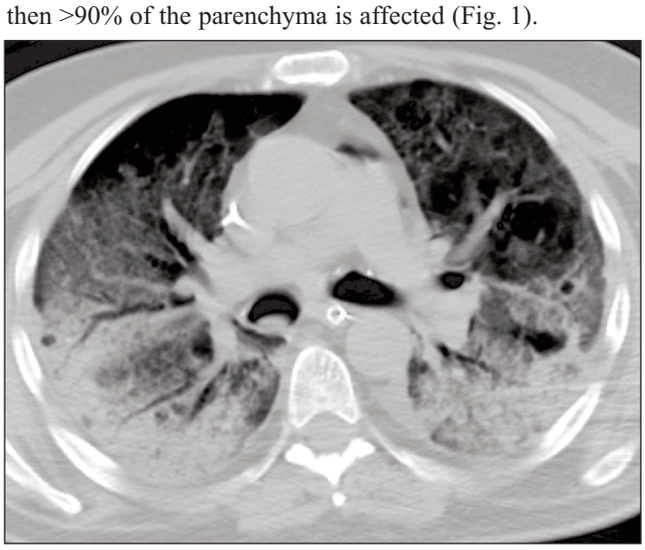

Figure 1. *High-resolution axial pulmonary CT scan showed diffuse bilateral central and peripheral multiple opacities of the pulmonary glass parenchyma together with the dominant consolidation of the posterior segments.*

Neurological examination performed on day 21 showed that pain stimuli elicited facial grimacing without any eye opening or limb movement observed, and he had flaccid tetraplegia and absent plantar reflexes. Brainstem reflexes were intact. Initial imaging evaluation with non-contrast CT of the brain revealed multifocal non-hemorrhagic white matter lesions in both cerebral hemispheres and cerebellum (Fig. 2).

Based on the deteriorating clinical and neurological status, the patient was started on intravenous methylprednisolone 1 g, based on a working diagnosis of COVID-19-related encephalitis, given the temporal presentation following a respiratory infection. After ruling out papilledema, a lumbar puncture was performed. Cerebrospinal fluid (CSF) showed IgG of 50.40 mg/L (normal range: 0–34.0 mg/L) with normal protein range. Gram staining of CSF was negative for bacteria and acid-fast bacilli. No detectable growth was noted in bacterial and fungal cultures. Cytology revealed no malignant cells. Inflammatory markers including D-dimer (2.6 mg/dL (normal range: 0–0.5 mg/dL)), and IL-6 (36.60 pg/mL) (normal range: 0–05.90 pg/mL)) were significantly elevated. Reverse transcriptase-polymerase chain reaction (RT-PCR) for CSF was not performed.

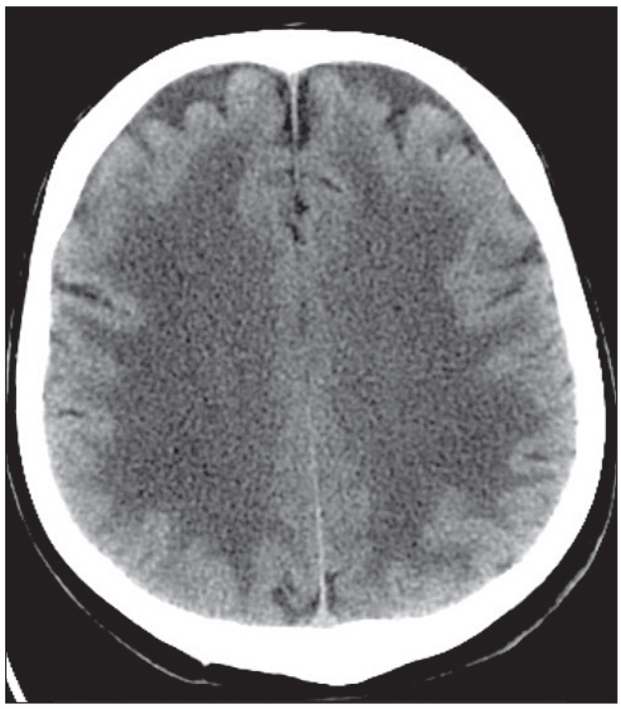

Figure 2. *An axial CT imaging of brain demonstrates hypodensity throughout the cerebral white matter*

Despite aggressive immunomodulatory measures, the patient's clinical and neurological status continued to deteriorate. A contrast-enhanced brain MRI performed on day 25 after hospital admission showed non-enhanced diffuse, bilateral, symmetric, confluent hyperintensities located in the deep and subcortical white matter with the involvement of the frontal, parietal, temporal and occipital lobes, as well as the brain stem, bilateral capsula interna and cerebellum, suggesting vasogenic edema. A microhemorrhage was found in corpus callosum, posterior limb of capsula interne of the left and basal ganglia on the right side. MRI showed non-diffusion restriction. The thalami showed no alterations. MRI angiogram and venogram of the brain were unremarkable (Fig.3).

A definitive diagnosis of COVID-19-related diffuse leukoencephalopathy with callosal microhemorrhages has been made, given the rapid clinical deterioration, progression of imaging characteristics, and CSF imaging. Therapy against edema continued. However, the patient's state rapidly became worse and he died after 16 days.

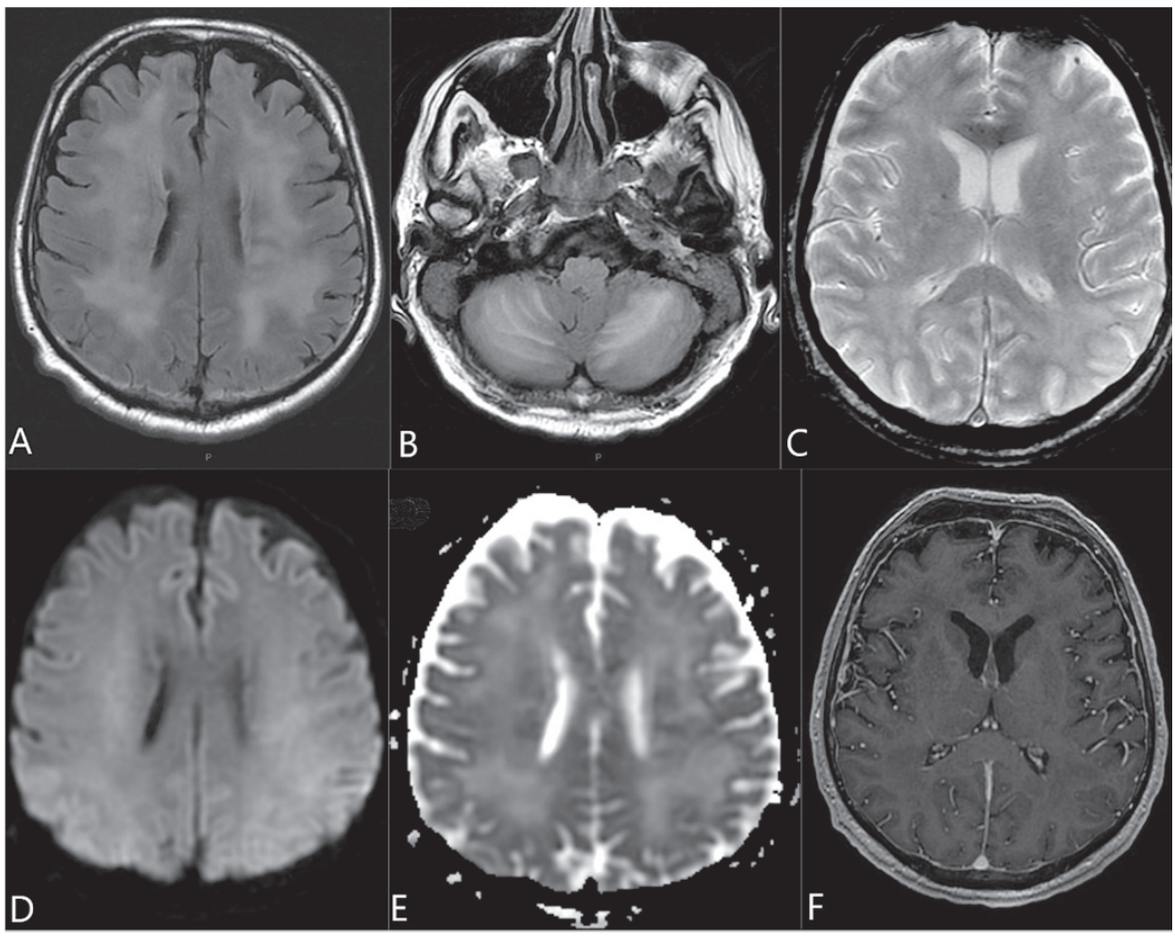

Figure 3. *An axial MR imaging of the brain. (A,B) FLAIR and (F) post-contrast T1-weighted images showed non-enhanced diffuse, bilateral, symmetric, confluent hyperintensities located in the deep and subcortical white matter and cerebellum, suggesting vasogenic edema. (C) T2-star images showed microbleeds in corpus callosum, capsula interne of the right and basal ganglia on the right side. (D,E) Paired diffusion-weighted imaging and apparent diffusion coefficient showed non-diffusion restriction.*

DISCUSSION

Recent studies have described abnormal brain imaging findings of microhemorrhages, multifocal white matter hyperintense lesions with variable enhancement, infarcts, hemorrhagic lesions, acute hemorrhagic necrotizing encephalopathy and inflammatory CNS syndromes including acute disseminated encephalomyelitis (ADEM).

Leukoencephalopathy and WM cytotoxic edema can be seen in critically ill patients in a variety of conditions, including patients with diffuse hypoxic-ischemic injury, posterior reversible encephalopathy, septic shock, acute disseminated encephalomyelitis, and various toxic metabolic causes [5,6].

Microhemorrhages have been reported previously in a number of locations including lobar, subcortical, deep, corpus callosum, pontine, and cerebellar [7,8].

A few studies have reported the splenium of corpus callosum as the predominant location for microhemorrhages, with or without oedema [4,9]. Microhemorrhages in the splenium of the corpus callosum have been reported in severe ARDS and high-altitude cerebral oedema, thought to be due to hypoxemia [10]. It is increasingly recognized that respiratory failure may be due to micro-emboli, and these may also affect the cerebral microcirculation resulting in microthrombosis and microvascular ischemia [11].

MRI of the brain in our patient with leukoencephalopathy and microhemorrhages revealed diffuse confluent symmetric white matter T2/FLAIR hyperintensities including brainstem and cerebellum, and scattered microhemorrhages with the predominant location in the genu of corpus callosum, without diffusion restriction and abnormal enhancement. As it was already said, microhemorrhages rarely occur in the corpus callosum, and even when they do it is usually in the region of spenium.

However, that was not the case with our patient and that makes this case report specific. These imaging findings are non-specific and can accompany several well-established leukoencephalopathies, such as acute hemorrhagic encephalomyelitis [12].

CONCLUSION

Neuroimaging findings in patients having COVID-19-associated neurological complications are being increasingly reported. Diffuse leukoencephalopathy with microhemorrhages is rare and often fatal neurological complication of COVID-19. Heightened clinical awareness and early imaging identification of diffuse leukoencephalopathy with microhemorrhages can provide clinicians with the opportunity to pursue more aggressive treatment options, thereby reducing fatal outcomes.

Sažetak

Uvod: Sve više se uočavaju neurološke komplikacije povezane sa SARS-CoV-2 infekcijom. Kompjuterizovana tomografija (CT) bez aplikacije kontrastog sredstva može u početku, kod difuzne leukoencefalopatije sa mikrohemoragijama, da pokaže ekstenzivne, prilično simetrične hipodenzne oblasti u supratentorijalnoj beloj masi i *corpus-u callosum*-u, dok magnetna rezonanca (MRI) pokazuje difuzne, konfluentne T2 hiperintenzitete i brojne mikrohemoragije predominantno subkortikalno u beloj masi i *corpus callosum*-u, bez restriktivne difuzije i bez postkontrastnog pojačanja intenziteta signala. **Prikaz slučaja**: Inicijalna imidžing evaluacija, pomoć nekontrastnog CT endokranijuma, otkrila je multifokalne nehemoragične lezije bele mase u obe velikomoždane hemisfere i u malom mozgu. MRI endokranijuma sa i.v aplikovanim kontrastim sredstvom pokazao je difuzni, bilateralni, simetrični, konfluentni T2 hiperintenzitet bez postkontrastnog pojačanja intenziteta signala, lokalizovan u dubokoj beloj masi, subkortikalno sa zahvatanjem frontalnog, parijetalnog, temporalnog i okcipitalnog režnja, kao i moždanog stabla, *capsula interna*-e obostrano i malog mozga, što ukazuje na vazogeni edem. Viđena je mikrohemoragija u *corpus callosum*-u, posteriornom kraku *capsula interna*-e levo i bazalnim jedarima na desnoj strani. MRI nije pokazao restrikciju difuzije. U talamusu nisu registrovane nikakve promene. MRI angiografija endokranijuma je bila nesignifikantna. Obzirom na brzo kliničko pogoršanje, progresiju *imidžing* nalaza i nalaza cerebrospinalne tečnosti, postavljena je definitivna dijagnoza difuzne leukoencefalopatije sa kaloznim mikrohemoragijama, povezane sa COVID-19. **Zaključak**: Difuzna leukoencefalopatija sa mikrohemoragijama je retka i često fatalna neurološka komplikacija COVID-19. Poremećaji svesti i rana identifikacija difuzne leukoencefalopatije sa mikrohemoragijama mogu pružiti kliničarima priliku da traže agresivnije opcije lečenja, čime se smanjuje mogućnost fatalnih ishoda.

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