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SINUS SAGITTALIS SUPERIOR THROMBOSIS TWO WEEKS AFTER COVID-19 INFECTION - A CLINICAL CASE IN A 60-YEAR-OLD PATIENT

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ABSTRACT

The thrombosis of cerebral veins and dural sinuses is rare in the clinical practice, often severe with a various clinical picture and neurological symptoms and potentially high mortality. Last year, in terms of the COVID-19 pandemic, the cases of thrombosis of cerebral veins and sinuses have increased, both as a complication of the viral infection and as isolated cases after vaccination against COVID-19. The thrombosis of the upper sinus sagittalis, as in other cases of intracranial thrombosis, often occurs with a gradual development of the clinical picture and imaging findings. The symptoms usually include severe headache, papilledema, and severe disturbances of consciousness as an expression of increasing intracranial pressure, seizures, and motor deficit, which is often bilateral.We present a clinical case of a 60-year-old man who 14 days after a COVID-19 infection with a bilateral pneumonia and coagulopathy, gradually manifested progressive cerebral, focal neurological symptoms and a meningeal syndrome. The performed imaging studies - computed tomography, contributed to the detection of the disease, visualized gradually increasing parenchymal lesions, which completely correlated with the deterioration of the neurological symptoms during the disease. The computed tomography with intravenous contrast enhancement (especially the venous phase) showed a significant diagnostic value and visualized the classic symptom of the empty delta sign as a result of occlusion of the lower part of the superior sinus sagittalis.

Key words: sinus sagittal thrombosis, cerebral venous thrombosis, COVID-19 infection, computed tomography, thrombocytopenia

PRESENTATION OF THE CLINICAL CASE

A 60-year-old man with concomitant diseases such as diabetes mellitus, who suffered from childhood of epilepsy with residual cognitive deficits, is presented. Two weeks before the clinical onset of the disease, he was treated for COVID-19 pneumonia with antibiotics, high doses of corticosteroids, heparin 20,000 IU daily and acetylsalicylic acid 100 mg. After discharge, the patient develops headache, photophobia, vomiting, severe disturbances of consciousness to coma (Glasgow Coma Scale 11 points), focal and generalized tonic-clonic seizures, meningeal syndrome, focal neurological deficit - right-sided damage to the n.poglossis and n.hy central type, right hemiplegia, total sensorimotor aphasia. In addition to neurological symptoms, fever up to 38 °C, generalized petechial rash, haematemesis, cough and wet wheezing were also observed. The subsequent clinical course of the disease, the gradual development and deterioration of the clinical symptoms ends fatally five days after the onset of symptoms.

The patient underwent complex laboratory and imaging tests, which were followed 24 hours in parallel with the clinical deterioration. The rapid antigen test and RT-PCR for SARS-COVID-19 RNA were negative. The hematological disorders from the laboratory tests are indicative -

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thrombocytopenia with a platelet count of 40 x10^9/l and a tendency to deteriorate to 25x10^9/l against the background of normal hemoglobin and erythrocytes, however, with leukocytosis 22.3x10^9/l with granulocytosis with olfactory lymphocytopenia. From the hemostasis profile: prothrombin time, INR, aPTT were normal, but D-dimer values were eight times higher. The biochemical blood tests showed high CRP values of 295.4 g/l, lactate dehydrogenase 561 U/l, hyperglycemia and normal values of liver enzymes, electrolytes, urea and creatinine. The chest radiography revealed evidence of bilateral interstitial pneumonia with not well differentiated reticulonodular opacities.

The most informative for the diagnosis was the computed tomography, which made it possible to monitor the progression of the pathological process and supratentorial lesions**. (Figures 1, 2, 3, 4)**

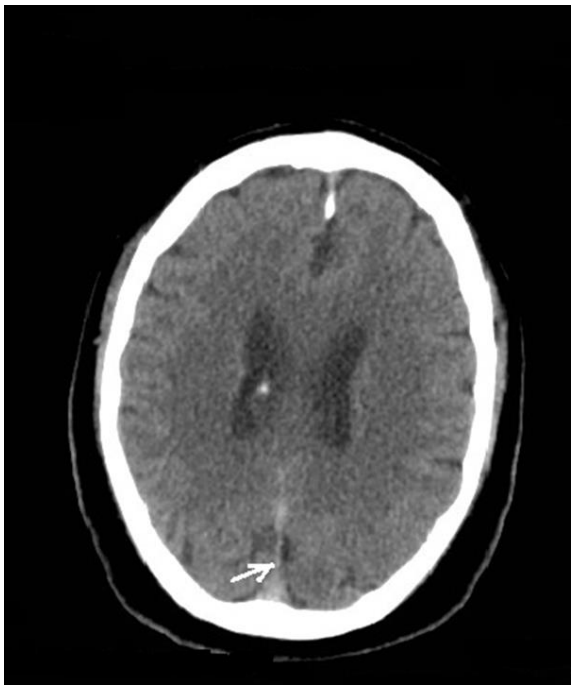

Figure 1. The first noncontrast CT examination performed at the 6th hour after the clinical onset of the disease visualized discrete nonspecific manifestations - abnormal hyperdensity in the area of the lower sinus sagittalis superior "cord sign" or "string sign", without showing pathological abnormalities in the brain parenchyma.

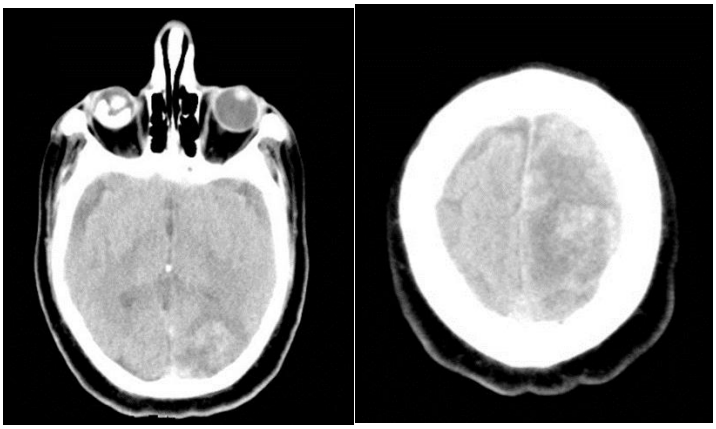

Figure 2. The second noncontrast CT scan of the brain after 24 hours shows hyperdense, hemorrhagic equivalent lesions in the subarachnoid spaces parietally bilaterally, as well as on the left side parietooccitally – an extensive area of increased density with hyperdense foci with an average density of 65 HU centrally and in the upper parietal lobe another one lesion with similar characteristics

This progression in the second control CT of the brain directly correlates with the clinical deterioration of the patient to coma (GCS 6t), quadriparesis, generalized seizures and meningeal syndrome.

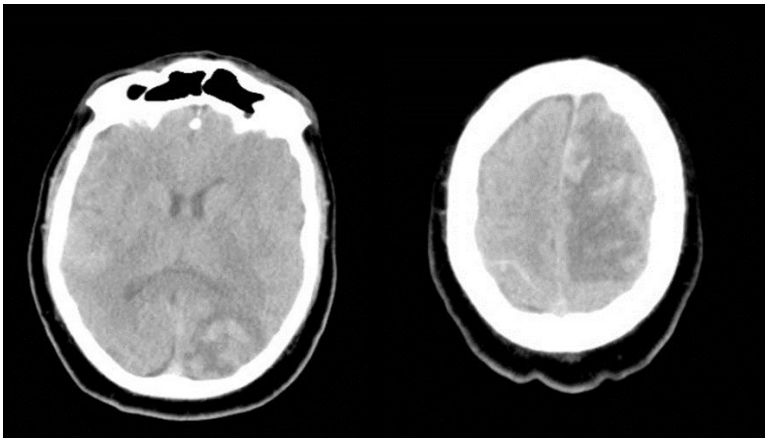

Figure 3. At the 48th hour after the clinical onset, the CT scan of the brain with intravenous contrast enhancement that was performed, showed the highest diagnostic value. Bilateral hemorrhages in the subarachnoid space, cerebral edema with dislocated interhemispheric fissure, with expansion of the extensive two hypodense zones with hyperdense central foci with a density of 65 HU parietally and parietooccitally were visualized.

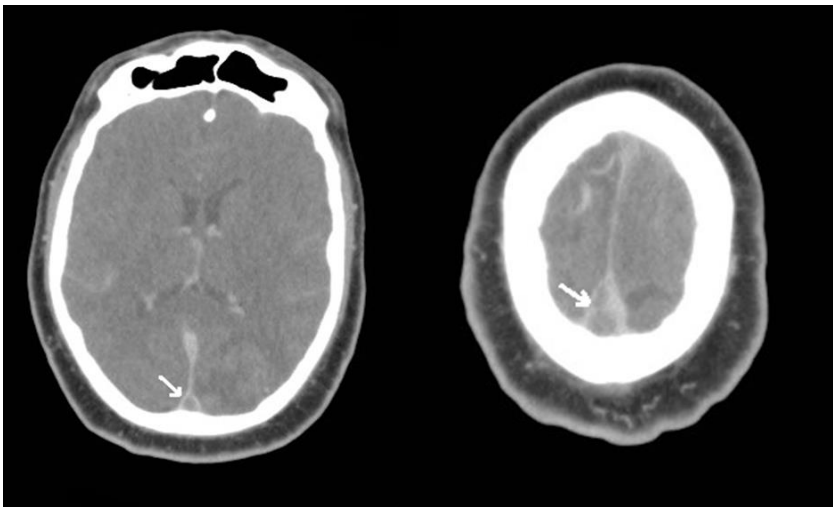

Figure 4. During the late venous phase of the study, the symptom of the empty delta sign (sinus sagittalis superior) specific for thrombosis was established as a result of occlusion of the lower part of the superior sinus sagittalis.

This, together with the clinical symptoms, laboratory tests, the most likely association with the recent COVID-19 infection, which led to the fatal coagulopathy in the case, helped to determine the diagnosis of superior sinus thrombosis.

The patient was promptly given resuscitation treatment with triple antibiotic therapy, correction of hematological disorders and coagulopathy, abnormalities in water-electrolyte and acid-base balance, hyperglycemia, hyperpyrexia, as well as antiedema and neuroprotective therapy. However, the patient's condition remained critical and ended fatally on the fifth day after the onset of the clinical symptoms.

DISCUSSION

The thrombosis of cerebral vessels and veins is much less common than arterial strokes. According to the AHA / ASA, its incidence in developed European countries and Australia is about 0.5 to 1/100 000 people per year of the total population, and the disease can often remain undiagnosed because of various reasons. (1) According to the European Stroke Organisation (ESO) results, the incidence of cerebral venous thrombosis is 1.32 / 100,000 people per year in Western Europe, which is higher in developing countries. (2) The distribution by gender shows a higher frequency in women, often in young people under 50, much more often in pregnant women or women taking oral contraceptives (1). The age distribution is also different from that of ischemic arterial stroke, and it is more common in children and young adults (2). The average mortality is about 5% and is most commonly caused mainly by fatal cerebral herniation, extensive hemispheric hemorrhagic infarction, less commonly status epilepticus, infection, and pulmonary embolism (2). Many risk factors are associated with cerebral venous sinus and vein thrombosis. They are divided into transient risk factors, such as oral contraceptives and other drugs or drugs with prothrombotic effects, pregnancy and puerperium, infections, especially those affecting the central nervous system or paranasal sinuses, ear and mastoid cells, dehydration and persistent risk factors that usually are prothrombotic medical conditions, including genetic thrombophilic diseases, antiphospholipid syndrome, myeloproliferative disorders, and malignancies. In about 13% of cases, the risk factors for cerebral venous thrombosis cannot be identified (2).

In connection with the COVID-19 pandemic and the increasing thrombotic complications and coagulopathy that occur as a manifestation of severe clinical courses of the infection, the incidence of cerebral venous sinus thrombosis is increasing, and a number of clinical studies are currently underway.

According to the results of a retrospective multicenter cohort clinical study in the city of New York (New York Metropolitan Cohort Study) of 13,500 patients with COVID-19 who were hospitalized between 1st March and 30th May, 2020.12 patients (8.8: 10,000) were diagnosed by imaging with cerebral venous thrombosis. The average age of patients was 48 years, and 25% were under 25 years of age. Men make up 66% of the studied patients. Previous prothrombotic risk was identified in only 17% of patients (breast cancer and deep vein thrombosis). However, traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, smoking) were identified in 58% of the study group (3).

A retrospective cohort study was subsequently conducted in the United States on 537,913 patients with a confirmed diagnosis of COVID-19 between 20th January, 2020, and 25th March, 2021.From them, 23 were diagnosed with cerebral venous thrombosis 14 days after diagnosis. The study showed that the absolute incidence of cerebral venous thrombosis in the 14 days following the diagnosis of COVID-19 was 42.8 / 1,000,000 patients, respectively. The incidence decreased rapidly in the following weeks, proving a causal relationship between COVID-19 and the thrombotic event (4).

The average age is 46.5 years, and the ratio of women to men is 69.6% to 30.4%. The risk is significantly higher in patients with a history of cardiovascular disease, particularly with an arterial vascular disease, rather than other prothrombotic factors for venous thrombosis. The mortality among patients after cerebral venous thrombosis in the two weeks after COVID-19 was 17.4% and was significantly higher than in patients with COVID-19 who did not have thrombosis or in patients with thrombosis not associated with COVID. (4) The COVID-19 infection has been shown to be associated with a significantly increased incidence of cerebral venous thrombosis compared to influenza patients or people who have been vaccinated with currently available mRNA and vector vaccines. Thrombocytopenia is also significantly more common two weeks after COVID-19 than after vaccine or influenza (4).

Our case report confirms the results of these studies - the patient is a man older than usual (60 years) with risk factors for cerebrovascular disease - diabetes mellitus, which was decompensated with manifestations of

ketoacidosis. This is a further evidence that the group of patients with cerebral venous thrombosis after COVID differs in demographics (age and sex) and prothrombotic risk factors from the usual prepandemic cases. In this case, the clinical manifestation of cerebral venous sinus thrombosis is 14 days after the onset of the COVID-19 infection, which is indicative for the severe clinical course of the disease and the development of severe coagulopathy with DIC syndrome.

The vascular-endothelial disease and coagulopathy prior to the COVID-19 infection, developed in the hyperinflammatory phase of the disease is the most likely etiopathogenetic mechanism in this patient. Studies have shown that concomitant thrombocytopenia, which occurred 14 days after onset, was also the result of a pathological intravascular activation of the coagulation cascade or of a previously administered high-dose heparin treatment such as heparin-induced thrombocytopenia, or both. It is generally accepted that thrombocytopenia is an indicative marker of the disease severity and a progressive decrease in the platelet count is associated with increased mortality, which in this case was indicative of a fatal outcome. The pathophysiology of thrombocytopenia in the COVID infection is on the one hand a suppression of thrombopoiesis in the bone marrow, and, on the other hand is the increased consumption of platelets in intravascular hypercoagulation in the stage of hyperinflammatory response. The immunomediated thrombocytopenia, in which the increased levels of autoantibodies and immune complexes can lead to platelet destruction, is further discussed (5). An important and basic guiding marker, however, remains the values of D-dimer, which in this case were eight times above normal.

In this case, the type of thrombocytopenia being heparin induced due to the previously administered high doses of unfractionated heparin was also discussed, and according to many publications it occurs much more often after administration of unfractionated than low molecular weight heparins. (7).

Paradoxically, severe heparin-induced thrombocytopenia, which occurs in 1 to 5% of heparin-treated patients, corresponds directly with an increased incidence of thrombosis (40% -50% of patients), both in cases of COVID infection and in other unrelated patients. (7). According to two clinical studies, it leads to venous thrombosis much more often than arterial thrombosis, with a ratio of venous to arterial events of 4:1 (7). This defines the use of therapeutic doses of anticoagulants as an important part of the treatment of COVID-associated coagulopathy for the prevention or treatment of thrombotic events. It includes cases of heparin-induced thrombocytopenia, which also requires anticoagulation at therapeutic doses, whether or not there is evidence of thrombosis (7).

Beyond the initial cause, however, the clinical course with the gradual unfolding of the clinical and imaging findings, remains typical of thrombosis of the superior sinus sagittalis, which is most important for the diagnosis and behavior. Headache has been reported as an initial symptom in 60–90% of the patients, but unlike subarachnoid hemorrhage, it usually begins subacutely within a few days (8). In our patient there was initially a headache, accompanied by photophobia, vomiting, turning into disturbances of consciousness to coma, seizures and a progressive focal neurological deficit. Within a few days, despite the resuscitation treatment, the case ended with death.

The dynamics of the cerebral bilateral parenchymal lesions, which arose in the left hemisphere to a greater extent, were monitored with CT, and the changes did not correspond to the arterial vascular basins. In addition to ischemic, hemorrhagic foci have been identified. In the first non-contrast CT they are not yet visualized, but nonspecific signs of thrombosis of the upper sagittal sinus are marked - "cord sign" or "string sign", which is found in 25% of patients with cerebral venous thrombosis, the venous vessel appears as compacted and hyperdense. (6). The most sensitive imaging modality was CT with intravenous contrast enhancement, which visualized the exact location of the thrombosis with the characteristic symptom of the empty triangle at the bottom of the superior sinus

sagittalis. The presence of an 'empty delta sign' in CAT is considered a pathognomonic sign of sagittal sinus thrombosis, despite the lack of an explanation for its occurrence (9). It is presented only by CT with intravenous contrast enhancement, which makes this diagnostic method indispensable in the diagnosis of cerebral sinus thrombosis.

Finally, in this and in all cases of patients with COVID infection and at high risk of cerebral venous thrombosis, early anticoagulant treatment with unfractionated or low molecular weight heparins plays the most important role. Given the higher mortality from cerebral venous thrombosis observed with COVID-19 infection, early initiation of anticoagulation in patients suspected or predisposed to it is crucial. 60% of the thrombosis patients treated with anticoagulants survive, which is a promising sign (10). In this case, in addition to the severe coagulopathy with DIC syndrome due to COVID, heparin-induced thrombocytopenia as a result of previously administered high doses of unfractionated heparin may play a role in the development of sinus sagittal thrombosis.

Conclusion: The reported clinical case clearly assigns into the increased trend towards thrombotic cerebrovascular complications during the COVID-19 pandemic. Globally, the different risk profile of patients for the development of cerebral venous thrombosis and the more severe clinical course of both COVID infection and thrombosis itself, leading to high mortality, are impressive. The clinical experience shows that the cerebral venous sinus thrombosis is a challenge for both diagnostic and therapeutic aspects, both before and during the COVID pandemic.

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