Diabetic ketoacidosis, cerebral venous sinus thrombosis and fulminant cerebral oedema in COVID-19 infection complicated by *Klebsiella pneumoniae* infection

Lindsey A Wallace ,[1] Sara E Hocker,[2] Hilary Dubrock,[3] Philippe Bauer[4]

[1]Critical Care Independent Multidisciplinary Program, Mayo Clinic, Rochester, Minnesota, USA
[2]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA
[3]Medicine, Mayo Clinic, Rochester, Minnesota, USA
[4]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Dr Lindsey A Wallace;
wallace.lindsey@mayo.edu

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SUMMARY

We present an unusual case of a woman in her 30s who was admitted for diabetic ketoacidosis (DKA) in the setting of newly diagnosed but late COVID-19 infection with associated *Klebsiella pneumoniae* infection.
Her altered mental status, out of proportion with her metabolic decompensation, revealed a superimposed cerebral venous sinus thrombosis (CVST) with fulminant cerebral oedema and ultimately brain death. This unusual and fulminant case of cerebral oedema in the setting of COVID-19 infection with bacterial infection, DKA and CVST was the perfect storm with multiple interwoven factors. It offered diagnostic and treatment challenges with an unfortunate outcome. This unique case is a reminder that it is important to consider a broad neurological differential in patients with COVID-19 with unexplained neurological manifestations, which may require specific neurointensive care management.

BACKGROUND

Both thromboembolic events and neurological manifestations are frequent in COVID-19 infection and portend a poor prognosis. However, the incidence of cerebral venous sinus thrombosis (CVST) in the setting of COVID-19 is rare.

CASE PRESENTATION

We present the case of a woman in her 30s who was admitted to our intensive care unit (ICU) for diabetic ketoacidosis (DKA) in the setting of newly diagnosed diabetes mellitus type II, altered mental status and COVID-19). The patient was unable to provide written consent due to her presentation and critical illness.

Her spouse found her confused and agitated for an unknown period before he brought her to an outside emergency department. Her spouse said the patient reportedly had a headache the day prior but denied any history of injury or trauma. On examination in the emergency room, heart rate was 118 bpm, respiratory rate was 43 bpm and Glasgow Coma Scale was 10 without any focal neurological deficit. On laboratory testing, serum glucose was 628 mg/dL (70–140 mg/dL), beta-hydroxybutyrate was 2.3 mmol/L (0–0.5 mmol/L), white cell count was 12 300×10^9/L ($3400–9600\times10^9$/L), platelet count 65×10^9/L ($157–371\times10^9$/L), pH 7.04 (7.35–7.45), bicarbonate 8 mmol/L (22–26 mmol/L), anion gap 26 (7–15), D-dimer 2264 ng/mL (<500 ng/mL), fibrinogen >1000 mg/dL (200–393 mg/dL). Lactate was 1.1 (0.5–2.2 mmol/L), troponin was 6 ng/L (<10 ng/L), then <6 ng/L after 2 hours. Pregnancy test with quantitative human chorionic gonadotropin was negative at 0.7 IU/L (<5 IU/L). Plasma ethanol, acetaminophen and salicylate levels were negative. Serum ethanol, acetone, isopropanol and methanol levels were negative. Urine drug screen and volatile screen were negative. Chest radiograph showed patchy bilateral multifocal pulmonary opacity consistent with viral or bacterial pneumonia. SARS-CoV2 PCR swab came back positive. Head CT without intravenous contrast showed no intracranial abnormality (figure 1). She was given 1 mg of intravenous lorazepam for agitation, intubated for airway protection and sedated with ketamine. A nurse-driven titratable insulin infusion with hourly glucose checks, sodium bicarbonate was initiated, and she received 4 L of normal saline for DKA. She was transferred to our institution directly to the ICU.

On arrival in the ICU, she remained intubated, ventilated and haemodynamically stable. On arterial blood gas, pH was 7.15, $PaCO_2$ 30 mm Hg (32–45 mm Hg), PaO2 91 mm Hg (83–108 mm Hg) and bicarbonate 10 mmol/L. Calculated PaO2:FiO_2 ratio was 227.5 mm Hg. She remained agitated and was kept sedated with fentanyl and propofol instead of ketamine for ventilator synchrony. Insulin infusion was continued. An arterial line and central line were placed. Chest radiograph showed again bilateral patchy airspace opacities consistent with acute respiratory distress syndrome. She received remdesivir, dexamethasone and tocilizumab for presumed severe COVID-19 pneumonia after emergent consultation with infectious diseases service. She was given deep vein thrombosis prophylaxis with enoxaparin 30 mg subcutaneously (patient's weight was 43.5 kg, body mass index was 17.65 kg/m^2).

Over the next 4 hours, she became progressively hypertensive reaching a blood pressure of 176/101 mm Hg for which she received 10 mg of labetalol intravenously. She stabilised for a few hours before she suddenly developed decerebrate posturing, with fixed and dilated pupils, no corneal or gag reflex and no spontaneous ventilation. Then she became hypotensive and was started on norepinephrine. She also developed polyuria and hypernatremia, with a sodium level of 163 mmol/L (135–145 mmol/L) consistent with diabetes

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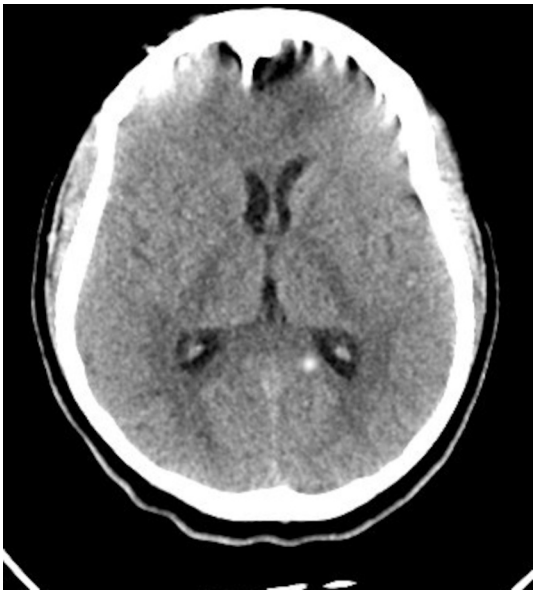

Figure 1 Initial non-contrast CT head with no acute intracranial abnormalities identified. Brain is normal in attenuation and morphology for patient's age. Ventricles and sulci were normal in size for patient's age.

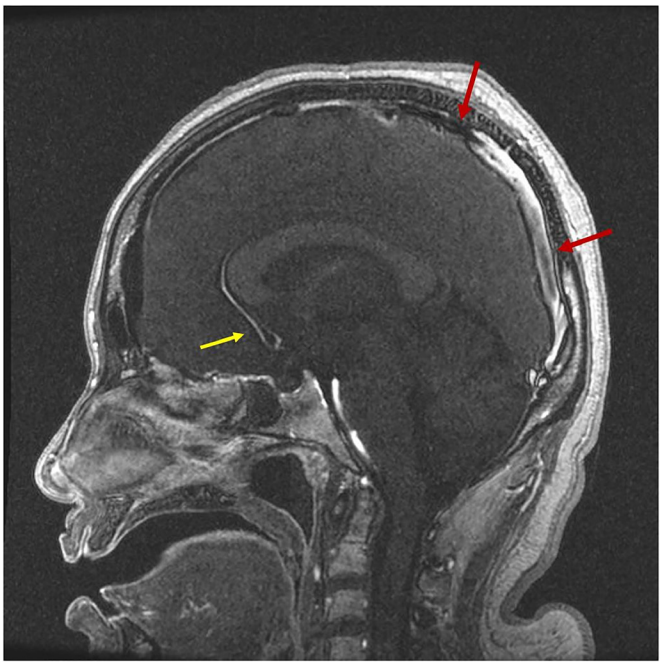

Figure 2 Sagittal reformatted magnetic resonance venography (MRV), three-dimensional maximal intensity projection (3D MIP) following gadolinium bolus demonstrated marked attenuation of intracranial blood flow including non-opacification of the deep internal cerebral veins and attenuated signal throughout the Circle of Willis (yellow arrow denotes attenuated flow within the anterior cerebral arteries). The superior sagittal sinus largely does not opacify with a minimal amount of opacification visualised posteriorly (red arrows).

insipidus for which she received desmopressin (four doses of 2 μg over 12 hours), and dextrose 5% water infusion which was initiated at 50 mL/hour, then increased to 125 mL/hour based on sodium levels and increased urine output. An emergent repeat head CT revealed diffuse cerebral oedema without herniation or haemorrhage. Neurology was consulted emergently. Sedation was stopped and mannitol was given. Meanwhile, her blood cultures came back positive for *Klebsiella pneumoniae* for which she was started on piperacillin–tazobactam.

Brain magnetic resonance venography (figure 2) was performed a few hours later and demonstrated diffuse cerebral oedema with marked attenuation of arterial flow voids at the skull base and non-opacification of the internal cerebral veins, vein of Galen and the dural venous sinuses. She was started on high-intensity heparin. Antiphospholipid serologies were normal (phospholipid Ab IgM 11.1, IgG <9.4 GPL). COVID-19 IgG antibodies came back positive and consistent with late COVID-19 infection. Remdesivir was discontinued, dexamethasone was maintained, and antibiotics were broadened to vancomycin and cefepime.

Head CT angiography (figure 3) the next day revealed worsening diffuse cerebral oedema with signs concerning for increased intracranial pressure, new duret haemorrhages of the midbrain and upper pons, non-opacification of the bilateral supraclinoid internal carotid and vertebral arteries and similar marked attenuation and thrombosis of the deep venous system and dural venous sinuses. She was declared brain dead soon thereafter.

DISCUSSION

This patient with previously undiagnosed diabetes mellitus type II presented initially with symptoms of DKA in the setting of newly diagnosed but already established COVID-19 infection based on positive serology. She was also diagnosed with a bloodstream infection soon after, likely a secondary infection linked to the known immune suppressive effect of both COVID-19 and diabetes mellitus, whereas bacterial coinfections are less frequent at the early phase of COVID-19.[1] Despite supportive measures aiming at correcting the DKA and intravenous antibiotics, the patient's neurological status deteriorated further, which was highly unusual. Diabetes mellitus is a known risk factor for severe COVID-19, and diabetic ketoacidosis has been observed frequently leading to increased mortality.[2 3]

Patients with COVID-19 are also at a higher risk for thromboembolic events with a higher risk of mortality, especially among patients who are hospitalised.[4 5] Neurological manifestations are frequent with COVID-19 and associated with a higher mortality in hospitalised patients.[6] Potential mechanisms include direct neuroinvasion (eg, meningitis, encephalitis), neuroinflammation (eg, acute necrotising encephalopathy), autoimmune disorders and other complications (eg, ischaemic stroke, endotheliopathy and hypercoagulability).[7] The incidence of CVST has rarely been reported in patients with COVID-19, and a high suspicion is necessary because of its potentially life-threatening condition and challenging diagnosis.[8] CVST has now been reported after adenovirus-based vaccine as well.[9] Prior to the pandemic, CVST was relatively rare, accounting for 0.5%–1.0% of cerebrovascular accidents in adults.[10] Usually patients present with headache, 90% of the time, and have underlying risk factors such as oral contraceptives, pregnancy, systemic infections, meningitis, cancer, antiphospholipid syndrome and many others.[11] It is important to note that this patient had been reporting of headache prior to presentation to support that her neurological changes may have been insidiously manifesting prior to her admission.

The patient was also encephalopathic, which ultimately lead to rapid intubation with ongoing sedation to control agitation and maintain ventilator synchrony in the context of hypoxemic respiratory failure. Additionally, her initial head CT was not alarming, which further supported a toxic/metabolic process

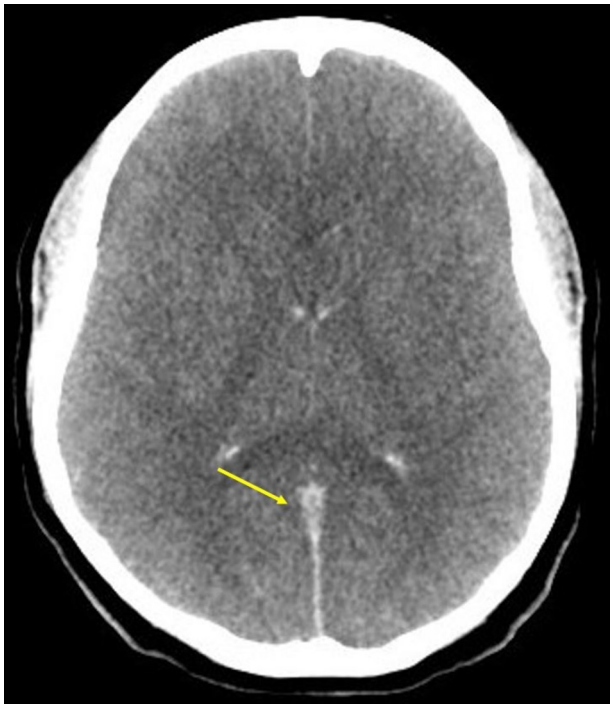

Figure 3 Non-contrast CT head demonstrated findings compatible with intracranial hypertension including loss grey–white differentiation and diffuse effacement of the ventricular system. Linear hyperattenuating signal along the cerebral falx posteriorly was compatible with associated venous engorgement (yellow arrow).

rather than a neurological process for her altered mentation on presentation, and the bloodstream infection would only be confirmed later. Meningitis was unlikely given the lack of pachymeningeal findings on brain imaging. Encephalitis could have explained the cerebral oedema from an acute infection; however, this patient's COVID-19 infection was established prior to her hospitalisation making the diagnosis of encephalitis less likely.

In general, acute cerebrovascular accidents may not be so infrequent in patients with COVID-19, especially in those who are severely infected and have pre-existing vascular risk factors such as diabetes mellitus.[12] Independent of COVID-19, the finding of cerebral oedema has been associated with deep cerebral venous thrombosis and poor clinical outcomes.[13 14] While cerebral oedema associated with DKA management in paediatric patients has been well documented in the literature, the role of specific aspects of DKA management in the development of cerebral oedema is extremely rare in adults and remains controversial.[15 16] Case reports regarding diabetic patients with COVID-19 and resulting cerebral oedema from CVST have not been published.

This unusual and fulminant case of cerebral oedema in the setting of COVID-19 infection with bacterial infection, DKA and CVST was the perfect storm with multiple interwoven factors. It offered diagnostic and treatment challenges with an unfortunate outcome. While this case may be unique, it is important to consider a broad neurological differential in patients with COVID-19 with unexplained neurological manifestations, which may require specific neurointensive care management. It is now well established that COVID-19 can be complicated by coinfections, secondary infections and venous and arterial thromboembolic events as well as metabolic decompensation such as diabetes mellitus. A high index of suspicion and frequent neuro checks should prevail during and after the initial onset of COVID-19 infection.

Learning points

- Thrombotic complications with COVID-19 are frequent.
- Cerebral manifestations of thrombosis are rare.
- Diabetic decompensation and secondary infections are frequent with COVID-19.
- Consider a broad neurological differential in patients with COVID-19 with unexplained neurological manifestations while maintaining a high index of suspicion.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD
Lindsey A Wallace http://orcid.org/0000-0001-7264-9704

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