CLINICAL VIGNETTE

Hypophysitis of Unclear Etiology in the Setting of COVID-19 Pneumonia

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Case

A 63-year-old woman with schizophrenia was brought to the emergency department by her caregiver with altered mental status and shortness of breath. She was admitted with a diagnosis of COVID-19 pneumonia and treated for acute, hypoxic respiratory failure with five-days of dexamethasone, remdesivir, and bilevel positive airway pressure. She required vasopressor support for 24 hours for distributive shock. Her mentation and shortness of breath improved, and she was discharged home with nasal cannula oxygen supplementation. Unfortunately, her mentation progressively declined after discharge. She stopped eating, taking her medications, and talking to family members, prompting a second emergency department visit two weeks later.

On her second presentation, she was hypothermic, bradycardic, hypotensive, and hypoxic (Table 1). Her physical exam was notable for periorbital swelling and facial puffiness. She was intubated for acute hypoxic respiratory failure and airway protection. She again required vasopressor support for distributive shock. She had detectable COVID-19 PCR and Klebsiella pneumoniae in respiratory cultures.

The patient did not have a primary care provider, and no medical records or prior laboratory studies were available. Per her family, she received monthly risperidone injections at a local mental health clinic for management of schizophrenia. At baseline, she was alert and oriented only to name, minimally conversant, and able to recognize close family members. She was dependent in some activities of daily living, needing assistance with walking and bathing and was fully dependent on instrumental activities of daily living. Her family reported a postpartum hemorrhage 27 years prior, after the birth of her eighth and last child. She required blood transfusions and was rushed to the operating room for an unclear surgical procedure. She was unable to lactate thereafter and no longer menstruated. She had never been treated with chronic steroids or immunotherapy.

Laboratory results included undetectable free T4, low free T3, low normal TSH, low random ACTH, low random cortisol, mild hyponatremia, low LH, low FSH, low prolactin, and undetectable IGF-1 (Table 1). These findings led to the diagnosis of panhypopituitarism with a clinical presentation suggestive of myxedema coma.

Pituitary MRI demonstrated a thickened infundibulum measuring up to 4mm, a partial empty sella, and a pituitary gland small in caliber (Figures 1 and 2). There was no evidence of a sellar or suprasellar mass, or acute hemorrhage or infarction. The posterior pituitary bright spot was present. The thickened infundibulum was concerning for hypophysitis, which prompted an unrevealing investigation of secondary causes of hypophysitis (Table 1). A pituitary biopsy was considered but not pursued.

A CT abdomen and pelvis was performed during her hospitalization but was unable to completely visualize or confirm a prior hysterectomy.

Given suspicion for adrenal insufficiency and myxedema coma, the patient was started on hydrocortisone 50 mg intravenously every 6 hours followed by a 200 mcg loading dose of intravenous levothyroxine. In the setting of hypopituitarism, her levothyroxine dose was titrated to 150 mcg daily to achieve a free T4 level in the upper range of normal. Her hospital course was complicated by an acute left lateral thalamus/internal capsule infarct with the identification of a patent foramen ovale and bilateral femoral deep vein thromboses. She was treated with a course of ceftriaxone for Klebsiella pneumonia. She was subsequently transitioned to a tracheostomy. Steroid dosing was tapered to hydrocortisone 15 mg orally once daily in the morning and 5 mg once daily in the afternoon.

The patient was discharged from the hospital to a long-term rehabilitation facility due to her mechanical ventilator dependence and need for intensive occupational and physical therapy. Per discussion with family, approximately one month following discharge she is recognizing more family members and attempting to communicate but unable to fully verbalize clear statements. She continues to receive artificial nutrition. Her facial puffiness and periorbital edema improved, and she has shown improved strength and purposeful movement of the upper extremities.

Discussion

We present a case of panhypopituitarism likely due to hypophysitis that presented as myxedema coma soon after diagnosis of COVID-19. Hypophysitis is a rare condition, with an estimated annual incidence of 1 in 9 million.[1] Establishing the etiology of

hypophysitis remains challenging. The gold standard is a pituitary biopsy, though it is not routinely done as it is unlikely to change management in most cases.[2] The causes of hypophysitis are broad and include autoimmune, systemic inflammatory, infiltrative, drug-induced, and infectious etiologies.[3]

The extrapulmonary manifestations of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have not been fully explored and continue to evolve. COVID-19 has been associated with hematologic, cardiovascular, renal, gastrointestinal, hepatic, neurologic, dermatologic, ophthalmologic, and diabetic complications.[4] SARS-CoV-2 primarily affects the lungs, using the angiotensin-converting enzyme 2 (ACE2) receptor as its mode of entry.[4] Both the hypothalamus and pituitary gland express ACE2, and thus can be potential targets for SARS-CoV-2.[5] Whether SARS-CoV-2 can directly cause hypophysitis is unknown.

Given the limitations of the patient's altered mental status and lack of medical reports, it was important to maintain a broad differential diagnosis for hypopituitarism. Given the finding of a thickened infundibulum, hypophysitis was strongly considered as a leading diagnosis. Yet hypophysitis typically presents with hypopituitarism in the setting of an inflamed pituitary and/or infundibulum alongside an enlargement of the pituitary gland. In contrast, our patient's pituitary gland was small in caliber with a partial empty sella. Thus, we explored broader etiologies for panhypopituitarism.

Causes of panhypopituitarism include congenital, neoplastic, infectious, vascular, inflammatory, and infiltrative etiologies, as well as from pituitary surgery and post-irradiation.[6] Congenital etiology was clinically ruled out as she had normal growth and development, conceiving and delivering 8 children. Pituitary neoplasm was ruled out by imaging studies, and the patient had no known history of pituitary surgery or radiation. Infectious etiologies were strongly considered. Of particular interest was her recent admission for COVID-19 pneumonia. After receiving a 5-day course of dexamethasone and remdesivir during her prior admission, she had detectable COVID-19 PCR two weeks after initial diagnosis, consistent with reports that suggest a median duration of detectable COVID-19 PCR 53.5 days after recovery.[7] The patient also had Klebsiella pneumonia based on respiratory cultures. There has been one case report of a pituitary abscess due to Klebsiella pneumonia causing mild hypopituitarism.[8] However, no pituitary abscess was noted on our patient's imaging. HIV was also considered and was negative on HIV-1/2 antigen/antibody screen. With regards to vascular pathologies, Sheehan's syndrome was considered given the history of significant post-partum hemorrhage. Our patient's imaging demonstrated a partial empty sella and a small caliber pituitary gland. For this reason, Sheehan's syndrome remained high on our differential diagnosis. Pituitary apoplexy was ruled out with no evidence of pituitary hemorrhage on imaging. Inflammatory and infiltrative etiologies were explored to evaluate for sarcoidosis, systemic lupus erythematosus, granulomatosis with polyangiitis, IgG4-disease, and lymphocytic hypophysitis. Serologies were negative.

To our knowledge, there is only one similar case of panhypopituitarism and hypophysitis presenting shortly after a diagnosis of COVID-19 pneumonia in the literature. Nonglait et al. described a 27-year-old otherwise healthy man who was found to have panhypopituitarism and hypophysitis six weeks after a diagnosis of COVID-19 infection.[9] His initial symptoms were considered mild, however he developed headaches, malaise, anorexia, and vomiting two weeks later. His labs demonstrated hyponatremia, hypocortisolemia, and hypothyroidism. In contrast to our case, he was found to have hyperprolactinemia and secondary hypogonadism. A subsequent MRI suggested hypophysitis, and he was started on steroids and levothyroxine replacement.

Other cases of pituitary dysfunction in the setting of COVID-19 infection have been reported. Three cases specifically reported a new diagnosis of diabetes insipidus, either during the acute phase of illness or several weeks after recovery from COVID-19.[10-12] There have also been several cases of pituitary apoplexy in the setting of COVID-19.[13-14]

The extrapulmonary manifestations of SARS-CoV-2 are continuing to evolve, and our case raises the question of whether there is a causal relationship between SARS-CoV-2 and hypophysitis. A pituitary biopsy was not completed, so we are unable to prove a causal relationship and these entities may be coincidental. However, given the presence of the ACE2 receptor in the pituitary, it remains a mechanistic possibility. Further studies will need to be conducted to determine if SARS-CoV-2 can lead to hypophysitis. Our case highlights the importance of evaluating for panhypopituitarism, particularly in critically ill patients in the setting of COVID-19 infection.

The patient's past history of significant post-partum hemorrhage with subsequent inability to lactate raises another intriguing facet. Sheehan's syndrome is often diagnosed much later in life with the mean duration between 2 and 40 years after the inciting event, due to nonspecific symptoms that are often misdiagnosed.[15] The triggering significant post-partum hemorrhage is thought to cause vascular spasms and/or thrombosis of the pituitary arteries leading to infarction. As a result of pituitary necrosis, patients may develop an empty sella over time. Half of patients can develop panhypopituitarism while the other half may develop partial hypopituitarism. One theory to explain the development of partial hypopituitarism is that collateral vasculature can bypass the necrotic areas of the pituitary gland to supply the residual, functioning tissue.[16] Partial hypopituitarism may produce enough pituitary hormones to sustain life while patients may exhibit nonspecific symptoms, including weakness, decreased axillary and pubic hair, and cognitive impairment, which may delay recognition of this syndrome.[15] As supported by her low prolactin levels and inability to lactate, our patient may have had partial pituitary dysfunction secondary to Sheehan's syndrome, which became

further compromised as a result of hypophysitis leading to frank panhypopituitarism.

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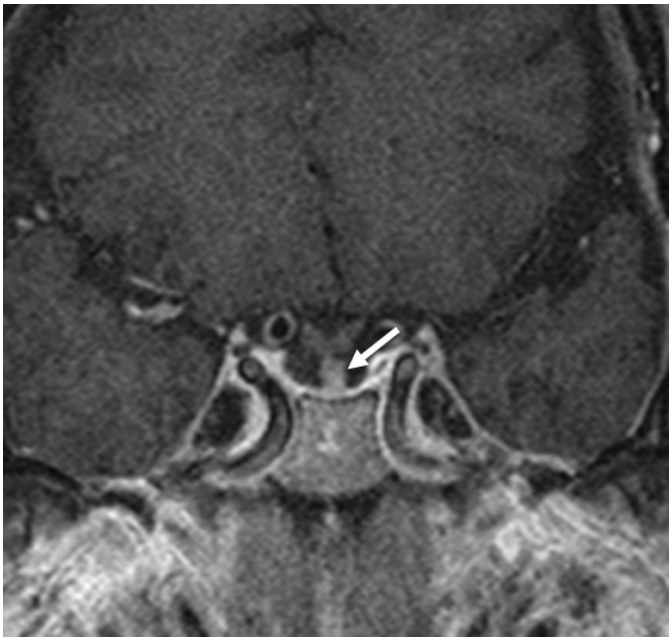

Figure 1 – Coronal postcontrast T1 weighted image of the sella demonstrates diffuse thickening of the infundibulum (arrow).

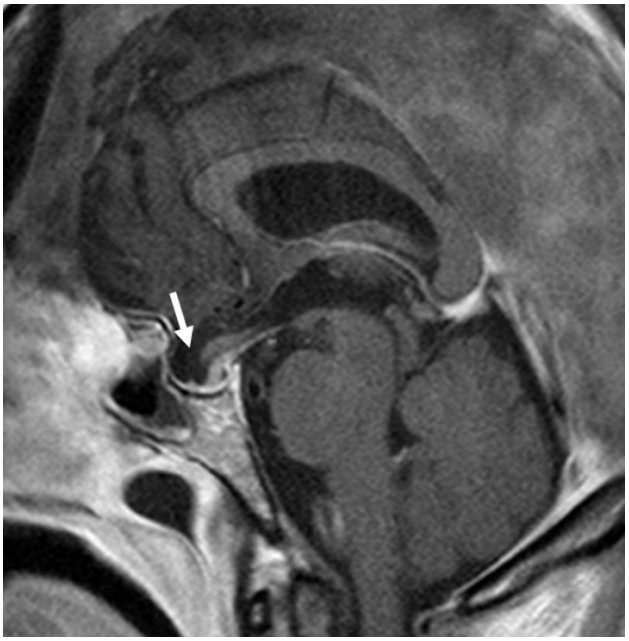

Figure 2 – Sagittal postcontrast T1 image of the sella demonstrates atrophy of the pituitary gland and partial empty sella turcica (arrow).

Table 1 – Vital signs and Laboratory results

Vital signs (units)	
Temperature (°C)	30.9
Blood pressure (mm Hg)	66/43
Heart rate (beats per minute)	41
O_2 saturation (%)	88
Laboratory results (normal range)	
TSH (0.3-4.7 mcIU/ml)	0.64
Free T4 (0.80-1.70 ng/dl)	<0.1
Free T3 (222-383 pg/dl)	48
ACTH (4-48 pg/ml)	6
Random cortisol (<6 mcg/dl)	6
Sodium (135-146 mmol/L)	133
LH (post-menopausal 16-63 mIU/ml)	0.1
FSH (post-menopausal 21-106 mIU/ml)	0.3
Prolactin (3-23.1 ng/ml)	1.6
IGF-1 (41-279 ng/ml)	<10
Serologies: ANA, anti-double stranded DNA, SSA antibody, SSB antibody, TPO antibody, thyroglobulin antibody, ANCA, pANCA, proteinase-3 antibody, myeloperoxidase antibody, IgG4 subclass, ACE level, HIV-1/2 antigen/antibody screen, CSF oligoclonal bands, CSF ACE.	All negative

Abbreviations: TSH – thyroid stimulating hormone, ACTH – adrenocorticotropic hormone, LH – luteinizing hormone, FSH – follicle stimulating hormone, IGF-1 – insulin-like growth factor-1, ANA – antinuclear antibody, TPO – thyroid peroxidase, ANCA – anti-neutrophil cytoplasmic antibodies, pANCA – perinuclear anti-neutrophil cytoplasmic antibodies, SSA – Sjögren's syndrome type A, SSB - Sjögren's syndrome type B, ACE – angiotensin converting enzyme, HIV – human immunodeficiency virus, CSF – cerebrospinal fluid

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