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DIAGNOSTIC DILEMMA
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A Cerebrospinal Case of Dyspnea

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PRESENTATION

A 63-year-old male presented to the emergency department of our hospital with a 1-week history of new onset of dyspnea. His past medical history was remarkable only for a recently diagnosed prolactin producing pituitary macroadenoma discovered during an emergency department visit for mild coronavirus disease (COVID-19) infection. He was being followed in the ambulatory endocrinology clinic for workup and had recently been started on oral cabergoline for treatment.

ASSESSMENT

On presentation to the hospital, the patient was hemodynamically stable, afebrile, with an oxygen saturation of 93% on ambient air. Blood work, including hemogram and serum biochemistry, was unremarkable, and a chest x-ray revealed no evidence of parenchymal infiltrates or pleural disease. A computed tomography (CT) pulmonary angiography scan revealed no evidence of pulmonary embolism; however, bilateral, patchy ground glass densities, predominating in the dependent segments of the lower lobes were noted (Figure 1A). A nasopharyngeal swab for COVID-19 PCR was negative and he was sent home with a 7-day course of oral antimicrobials (amoxicillin and clavulanic acid 875 mg/125 mg twice daily and doxycycline 100 mg twice daily) and a working diagnosis of community acquired pneumonia.

The patient returned to the emergency department 2 weeks later with persistent dyspnea and new onset dizziness despite completing his course of antimicrobials, and a 10-day trial of oral prednisone prescribed by his primary care physician. Consultation was requested with the internal medicine service for refractory pneumonia. On history, the patient reported new orthopnea, a non-productive cough that was worse when lying supine, and new rhinorrhea. There was no history of fever, headaches, weight change, or visual disturbances. There was no history of gastroesophageal reflux disease or prior aspiration events.

On physical examination, the patient was hemodynamically stable, afebrile, and had an oxygen saturation of 95% on ambient air. There was no evidence of orthostatic changes in his vital signs, and complete cardiac and respiratory exams were non-contributory. Electrocardiogram and serum high-sensitivity troponin T cardiac enzymes were within normal limits.

Because of the patient's dizziness and known history of a pituitary macroadenoma, we evaluated his serum thyroid stimulating hormone (0.55 mU/L, reference range 0.40-4.5 mU/L), early morning cortisol (392 nmol/L), and prolactin (2.4 ug/L, reference range 2.7-16.9ug/L). Repeat chest x-ray revealed faint opacities in the right midlung zone, concerning for ongoing parenchymal inflammation. A repeat nasopharyngeal swab for COVID-19 polymerase chain reaction remained negative.

On deeper questioning, the patient reported significant frustration related to new rhinorrhea. There was no prior history of allergic rhinitis, or other symptoms of an upper respiratory tract infection. He described clear, unilateral rhinorrhea that was precipitated by leaning forward (when brushing his teeth) and coughing. The patient demonstrated this to the clinical team by leaning forward, whereby drops of clear fluid trickled from his left nare (Figure 2, Video). The collected nasal fluid was positive for β_2-transferrin, consistent with the presence of cerebrospinal fluid (CSF).

Non-infused CT of the facial bones and sinuses revealed an air-fluid level in the sphenoid sinus and loss of bone involving the sellar floor (Figure 1B). Magnetic resonance imaging of the brain and sinuses with contrast revealed a

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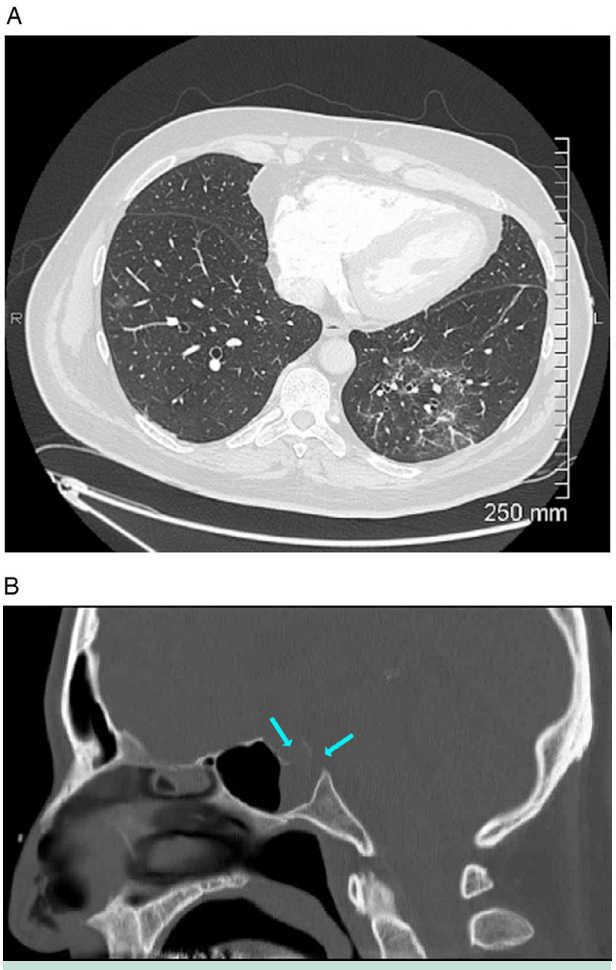

Figure 1 (**A**) Axial computed tomography of the thorax with contrast showing patchy consolidative and ground glass changes in the dependent lung zones. (**B**) Sagittal computed tomography of the head showing (blue arrows) defect in the floor of the sella and in the upper clivus and posterior wall of the sphenoid sinus caused by the pituitary macroadenoma.

reduced macroadenoma tumor bulk within the sella turcica and within the posterior left sphenoid sinus with erosion of the posterior wall and floor of the sella turcica.

DIAGNOSIS

Taken together, the poor response to antimicrobials, presence of CSF leak, and resolution of symptoms following surgical repair of the CSF leak suggest the dyspnea and radiographic findings were in fact diagnostic of a chemical cerebrospinal fluid pneumonitis.

Cerebrospinal fluid rhinorrhea is a rare and serious clinical manifestation of a pathological defect of the skull base resulting in CSF leaking through the nostril. Open communication between the subarachnoid space and the sinuses portends a risk for catastrophic complications, including meningitis, intracranial abscesses, and intracranial hypotension.

Typically, CSF leaks are categorized as traumatic or atraumatic, with 80% occurring due to craniofacial trauma and the remainder resulting from iatrogenic injury and malignancy.[1]

The characteristic presentation of CSF rhinorrhea is unilateral, positional, clear, watery nasal discharge, as seen in our patient. Patients often report symptoms that are exacerbated by a head-dependent position, giving rise to the "tea pot" sign. Cerebrospinal fluid rhinorrhea is often thought of as being clinically silent in the absence of infectious complications. Drainage may be confused with allergic and non-allergic rhinitis, and clinicians must have a high index of suspicion for potential CSF rhinorrhea.[1]

Diagnostic confirmation of CSF rhinorrhea remains challenging. There remain few biochemical markers to confirm the presence of CSF in nasal discharge. The β2 transferrin assay was first reported in 1979 as a safe and non-invasive method of screening patients with suspected CSF leaks.[2] It remains highly sensitive (99%) and specific (97%) and is considered the gold standard for the diagnosis of suspected CSF rhinorrhea.[2] The use of nasal secretion glucose concentrations is associated with both high false-positive and negative results due to many limiting factors, including fluctuations of serum glucose, bacterial contamination of nasal secretions, and assay sensitivity, and as such is no longer recommended for clinical use.[3]

Although uncommon, spontaneous CSF rhinorrhea may occur in the context of giant invasive pituitary macroadenomas, due to direct extension and erosion of the skull base. Additionally, the initiation of a dopamine agonist may result in regression of a pituitary adenoma and the development of a communicating fistula.[4] In our case, the patient's prolactinoma had eroded his skull base and was confirmed on neuroimaging to have regressed on cabergoline treatment, leading to a pathway for CSF leakage and thus his resulting rhinorrhea.

In a 2012 review, 52 patients with pituitary adenomas were identified as having spontaneous or medication-induced CSF leaks. Forty-two patients (81%) had a prolactinoma, and 73% developed CSF rhinorrhea following induction of medical therapy, providing support for the proposed mechanism in our case.[5]

To date, there remains a paucity of data on CSF-induced chemical pneumonitis. We postulate that the presence of this patient's clear CSF rhinorrhea, combined with periods of recumbency, led to a chronic aspiration phenomenon and associated pneumonitis, which would explain his dyspnea and radiographic findings. A 2020 retrospective case series reported 6 patients with chronic reversible pneumonitis attributed to spontaneous CSF leaks.[6] Similar to our report, the case series aimed to underscore the importance of maintaining a high index of suspicion for CSF rhinorrhea and its potential adverse pulmonary sequelae. Our report is the first to describe an acute presentation of dyspnea, orthopnea, and aspiration pneumonitis as the presenting symptoms of CSF rhinorrhea.

Figure 2 Leak of clear fluid from the left nare upon forward head tilt.

MANAGEMENT

The patient was referred to the otolaryngology service of our hospital for evaluation and underwent a transsphenoidal resection of the pituitary tumor and repair of the CSF leak. He was seen 3 weeks after surgery in the ambulatory internal medicine clinic, where he reported complete resolution of his rhinorrhea, exertional dyspnea, and orthopnea.

We thus report here a diagnostic dilemma surrounding a common clinical presentation of dyspnea, for which a comprehensive history and physical examination allowed identification of a rare but treatable etiology. This case illustrates the importance of detailed evaluation when faced with cases of dyspnea after empirically treating more common causes. Although a rare entity in and of itself and even rarer as a cause of pneumonitis, CSF rhinorrhea should be considered in the appropriate setting, in order to prevent both catastrophic central nervous system infections and the development of chronic lung diseases.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.06.022.

APPENDIX. SUPPLEMENTARY DATA

Video: Leak of clear fluid from left nare upon forward head tilt.