

CASE REPORT

Unraveling a Diagnostic Enigma: Navigating an Intricate Case of Spontaneous Cerebrospinal Fluid Rhinorrhea

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ABSTRACT

Cerebrospinal fluid (CSF) rhinorrhea is a relatively rare medical condition characterized by the drainage of CSF through the nasal cavity. Cerebrospinal fluid leakage can be attributed to a plethora of different causes, mostly traumatic or iatrogenic, but it can also be spontaneous. Due to its rare entity, CSF rhinorrhea is often a diagnostic trap and can be misdiagnosed and mistreated as rhinosinusitis or allergic rhinitis. This can result in severe complications, such as meningitis, which could potentially have life-threatening consequences if not accurately identified and managed. In this case report, a 53-year-old Caucasian woman presented at the emergency department with symptoms of headache, fever, transparent nasal discharge from her left nostril when leaning forward and mild neck stiffness. Based on the patient's clinical presentation and physical examination findings, there was a high suspicion of central nervous system infection and cerebrospinal fluid leakage. A lumbar puncture confirmed the diagnosis of meningitis, while imaging exams, including computed tomography (CT) and magnetic resonance imaging (MRI) scans, revealed a fistula between the posterior wall of sphenoid sinus and the subarachnoid space. Additional findings included an empty sella turcica, suggesting a potential underlying cause for this condition and an incidental meningioma near the area of leakage. The patient received empiric intravenous antibiotic therapy and was discharged after ten days. She was referred to the neurosurgical department for surgical repair of the CSF leak and removal of the meningioma, in line with appropriate treatment guidelines. This study highlights the importance of promptly identifying and thoroughly investigating potential causes of CSF leakage to provide appropriate medical management.

Keywords: CSF rhinorrhea, empty sella turcica, meningitis, sphenoid sinus fistula, spontaneous CSF leakage.

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ABBREVIATIONS

CT: computed tomography

CSF: cerebrospinal fluid

ESS: empty sella syndrome

MRI: magnetic resonance imaging

MR: magnetic resonance

PCR: polymerase chain reaction

INTRODUCTION

Cerebrospinal fluid is a clear, odorless and colorless plasma-like fluid that cushions the central nervous system, supports cerebral physiology and maintains brain homeostasis (1). It is an ultra-filtrate of plasma, primarily secreted by the choroid plexuses, which flows through the ventricular system into the basal cisterns and the subarachnoid space surrounding the spinal cord (2, 3). The reabsorption of the CSF into the blood circulation is executed by arachnoid villi and granulations that protrude into the dural sinuses based on a pressure-dependent gradient (1, 4).

Cerebrospinal fluid rhinorrhea is a rare condition characterized by the leakage of CSF from the nose, due to defects in the dura mater, skull base, or sinus mucosa. Persistent unilateral rhinorrhea occurs when there is a direct communication between the subarachnoid space and the nasal cavity. A fistula between the dura and the skull base permits CSF discharge through the nasal passages (5).

Cerebrospinal fluid rhinorrhea can be categorized as spontaneous, trauma-related or iatrogenic, with the latter most commonly associated with skull base surgery (6).

Traumatic CSF rhinorrhea is frequently observed after head injuries and can be categorized as either accidental or non-accidental (5). In contrast, spontaneous CSF rhinorrhea—which accounts for approximately 41% of all cases; it arises without a preceding identifiable cause but is often associated with underlying factors such as congenital skull base malformations or weakening of the dural tissue (7).

This condition is frequently misdiagnosed due to symptom overlap with chronic sinusitis or allergies, which can lead to delays in appropriate treatment.

Early diagnosis is crucial, given the risk of serious complications such as pneumocephalus, meningitis and brain abscess formation (8).

CASE PRESENTATION

This 53-year-old female patient initially presented with symptoms of headache, fever and unilateral nasal discharge, while bending forward or straining. The onset of nasal discharge began approximately one month before the development of headaches and fever. Following a temperature spike to 38°C and worsening headache intensity, the patient sought medical attention. Given this constellation of symptoms, there was concern that the condition might be more serious than a typical upper respiratory tract infection. Consequently, she was referred to our hospital for a comprehensive assessment.

At the emergency department, an internal medicine specialist and a neurologist conducted a thorough review of the patient's medical history and clinical presentation. She had a known history of hypertension and was on Telmisartan 80 mg. No other significant medical conditions were reported.

Upon arrival, the patient had a body temperature of 38°C and reported worsening headaches. Examination of the discharge from her left nostril revealed a clear, transparent appearance. She denied any weight changes, galactorrhea, or visual disturbances. A sample of the nasal discharge was collected for further analysis.

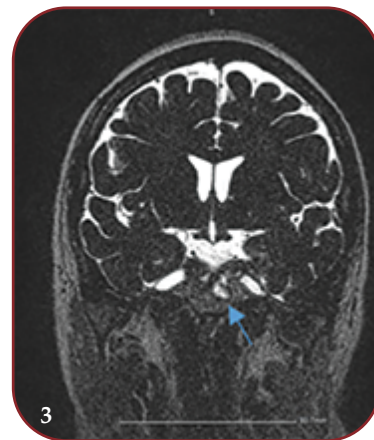
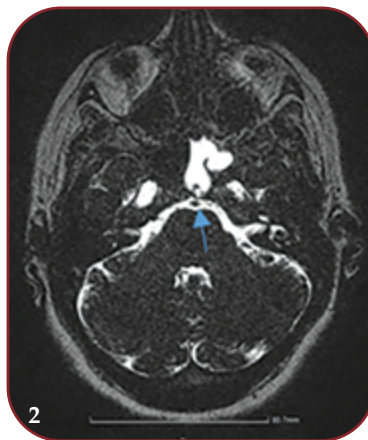
During physical examination, mild neck stiffness (nuchal rigidity) was noted, while Kernig's and Brudzinski's signs were negative. No additional abnormalities were observed.

Based on her symptoms and physical findings, there was a strong suspicion of CSF rhinorrhea and meningitis. Since trauma is a frequent cause of both CSF leaks and meningitis, the patient was asked about any recent injuries. Although she denied any obvious trauma, she recalled experiencing a severe headache after a nasal swab for a rapid COVID-19 test approximately one year earlier.

A computed tomography (CT) scan of the head revealed an osseous defect in the posterior wall of the sphenoid sinus, characterized by rounded pits, sclerotic scalloped margins and fluid accumulation with a fluid level resembling CSF (Figure 1).



FIGURE 1. Axial computed tomography bony image showing a defect in the floor of the middle cranial fossa which was resulting in a cerebrospinal fluid leak into the pneumatized sphenoid sinus



FIGURES 2, 3. Axial and coronal heavy T2 images (cisternography) pointing out the fistula (arrows).

A lumbar puncture confirmed the diagnosis of meningitis, revealing an elevated white blood cell count (1260 cells/ μ L) with a predominance of polymorphonuclear cells (83%). Cerebrospinal fluid analysis showed elevated protein levels (92.1 mg/dL) and decreased glucose (40 mg/dL). Polymerase chain reaction (PCR) testing was conducted to identify the pathogen, along with a complete blood count, blood cultures and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate.

Expert opinions from multiple disciplines were sought for the comprehensive management of this complex case, including specialists in neurology, neurosurgery, otolaryngology, radiology and internal medicine. The patient was admitted to the internal medicine department, where intravenous antibiotics were promptly initiated to treat the meningitis and prevent complications prior to considering surgical intervention.

Empirical broad-spectrum intravenous antibiotics were started to cover the common pathogens associated with meningitis. The patient was given ceftriaxone (2 g every 12 hours), vancomycin (500 mg every six hours) and metronidazole (500 mg every eight hours) to include anaerobic coverage due to the communication between the sphenoid sinus and the subarachnoid space. Unfortunately, PCR and CSF cultures failed to identify a specific causative organism.

In addition to antibiotics, the patient received intravenous fluids and close monitoring of vital signs to maintain hemodynamic stability. The na-

sal fluid tested positive for beta-2 transferrin, a highly specific marker for CSF, confirming the diagnosis. Cytological analysis of the CSF revealed no malignant cells, making a neoplastic cause of the leak unlikely.

To better evaluate the extent and location of the CSF leak, further imaging was performed, including a magnetic resonance imaging scan (MRI) and MR cisternography. Magnetic resonance cisternography confirmed a fistula extending into the left sphenoid sinus through an osseous defect in the posterior wall (Figures 2, 3). A T1-weighted sagittal MRI also showed an empty sella (Figure 4). There was no evidence of meningocele, encephalocele, intracranial hypertension, tumor, or trauma. A meningioma identified in the left temporal lobe appeared unrelated to the CSF leak (Figure 5).

The patient's fever resolved within 48 hours of treatment and by the sixth day of hospitalization she had no signs of rhinorrhea or other symptoms. She remained clinically stable and was discharged on the tenth day with a prescription for prophylactic amoxicillin-clavulanate to reduce the risk of recurrent meningitis.

After the successful treatment of meningitis, surgical intervention was deemed necessary to repair the CSF leak and resect the coexisting meningioma. She was referred to a specialized center for further neurosurgical evaluation and management.

During multidisciplinary discussions, several potential causes of the CSF leak were considered,

FIGURE 4. T1-weighted sagittal magnetic resonance imaging (MRI) image demonstrating an empty sella, with the pituitary gland being the white strip (blue arrow) compressed against the floor and posterior wall of the otherwise empty sella

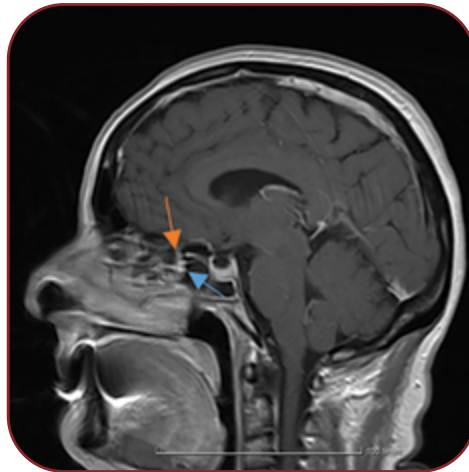
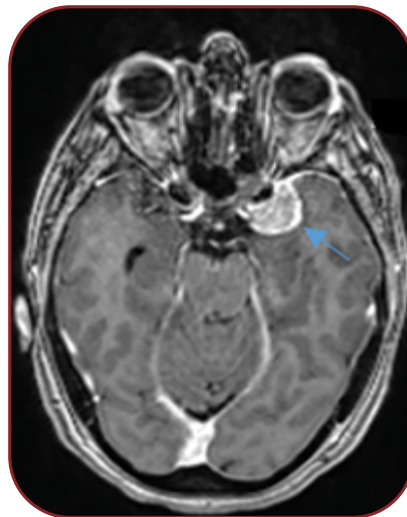


FIGURE 5. T1-weighted gadolinium-enhanced sequence showing a homogenously strongly enhancing meningioma at the temporal lobe



including the presence of an empty sella, possible trauma from the nasal swab and the adjacent meningioma.

DISCUSSION

Cerebrospinal fluid rhinorrhea is classified based on its etiology into two main categories: traumatic, which may be surgical, non-surgical, or iatrogenic, and non-traumatic (spontaneous) (9).

Traumatic CSF rhinorrhea accounts for approximately 90% of CSF leaks (10) typically caused by head trauma (skull-base fractures or facial fractures) (2), with the most common fracture sites being the frontal sinus, followed by the sphenoid and the ethmoid sinuses (11). In their retrospective study, Anghel *et al* demonstrated that the majority of craniofacial injuries involved the nasal region and were predominantly attributed to human aggression (12).

Iatrogenic CSF leaks usually occur post-operatively as a result of specific surgical procedures, with endoscopic sinus surgery and transsphenoidal hypophysectomy being the most frequently implicated (9).

The timepoint of CSF leakage varies, often appearing within 48 hours post-trauma. However, it can also be delayed and become apparent one week after trauma (13), with the majority of delayed cases manifesting within the first three months (10).

Our patient denied any history of endonasal or intracranial surgery, head or nasal trauma/injury. However, she reported experiencing an excruciating headache following a COVID-19 nasal swab test one year ago. It is important to note that she had undergone multiple forceful swab tests as part of her daily work requirements.

Although rare, documented cases have linked nasal swabs to CSF leakages. The safety and proper technique of nasopharyngeal swab tests, which have long been a part of our diagnostic protocols, are sometimes overlooked.

The first reported case of iatrogenic CSF leakage involved a woman in her 40s who developed unilateral rhinorrhea and symptoms of meningitis shortly after undergoing a nasopharyngeal swab for SARS-Cov-2 testing. Imaging revealed a pre-existing encephalocele in the right ethmoid fovea (seen on a 2017 CT scan) and a new pseudomeningocele in the right sphenoid wing, indicating that the test traumatized the preexisting encephalocele rather than creating a new osseous defect (14).

Another similar case involved a 59-year-old man with persistent CSF rhinorrhea following a nasal swab. The CT scan of the brain showed a defect in the sella turcica on the lateral wall and an abnormal connection between the left sphenoid sinus and the left middle cranial fossa. A follow-up MRI scan confirmed these findings and also detected an encephalocele protruding through the skull-base dehiscence. The authors supported that the inappropriate angle and depth of the nasal swab ruptured the mucosa bordering the pre-existing encephalocele, leading to CSF drainage (15).

Contrary to the aforementioned cases, where the swabs disrupted a pre-existing intracranial pathology, there have been reports of nasopharyngeal swabs directly causing CSF leaks. Kacemi *et al* described the case of a 48-year-old man who de-

veloped CSF leakage and encephalocele herniation inside the sphenoid sinus due to bony deformity on its inferolateral wall. Remarkably, there was no evidence of existing encephalocele before the nasopharyngeal swab or any other predisposing factors that could lead to intracranial abnormalities (16).

Another case involved a 40-year-old man who developed rhinorrhea after undergoing a nasal swab test for COVID-19, during which he felt something "cracked". It was discovered that he had a bony defect in the superior and lateral wall of the right sphenoid sinus, even though there was no preexisting skull-base dehiscence (17).

Further reports have linked cribriform plate defects with CSF leakage following nasopharyngeal testing in patients without prior sinonasal or skull-base pathology (18-20). In our case, while there is strong suspicion, a definitive connection between the swab and the sphenoid fistula is difficult to confirm, especially since most traumatic leaks occur within three months. The patient recalls the painful swab test occurred about a year ago but is unsure of the exact timeline.

Spontaneous CSF rhinorrhea can be attributed to various factors, such as tumor-related osseous erosion and skull-base defects, congenital deformities with accompanying lesions like meningoencephaloceles, empty sella syndrome (ESS), or hydrocephalus (both obstructive or communicating) (2). Risk factors exacerbating these clinical conditions and contributing to CSF leaks include obesity, sex (with a female predisposition), increased intracranial pressure and obstructive sleep apnea (21).

Our patient was not overweight, had no history of weight change and showed no clinical signs of intracranial hypertension such as blurry vision, double vision, papilledema, dizziness, nausea, vomiting, or tinnitus. She also denied galactorrhea or visual field defects. Furthermore, she had no history of headaches or hypopituitarism symptoms. As we previously mentioned, an MRI scan revealed the presence of a meningioma near the area of leakage. However, the location alone does not fully explain the development of a sphenoid sinus fistula. Additionally, on MRI, it was noted that she had an empty sella turcica indicating the missing key of this diagnostic puzzle. Generally, empty sella turcica and sphenoidal osseous impairments seem to be inextricably linked,

making ESS a diagnostic possibility in patients with non-traumatic CSF rhinorrhea.

The presence of bony defects in patients experiencing spontaneous, non-traumatic leaks may be associated with chronic undiagnosed intracranial hypertension (often related with radiographic evidence of an empty sella). This condition can weaken the fragile anatomical sites of the skull base (22).

The obstruction of CSF absorption, mostly at the arachnoid villi, raises CSF pressures and promotes the meningeal herniation and CSF circulation through the sellar diaphragm. The upraised intracranial pressure contributes to the genesis of high CSF hydrostatic forces that use as "egress windows" the areas of skull that are characterized by susceptibility, thinness and weakened resistance to pressure (23).

The development of sphenoidal fistulas most commonly occurs at the junction between the anterior portion of the lateral wall of the sinus and the floor of the base of skull, as well as in middle portion on sidewall. On the other hand, fistulas in posterior wall are very rare (24).

Several clinical reports link ESS with sphenoidal fistulas. In a published case from 2014, a 59-year-old woman presented to her primary care physician with symptoms of one week rhinorrhea, fever, headache and neck stiffness. A CT cisternogram revealed an osseous impairment in the lateral wall of the right sphenoid sinus, while subsequent MRI scan confirmed a diagnosis of ESS without detecting any other intracranial abnormalities (22).

In a similar case, a patient had been experiencing CSF rhinorrhea for four months. The MRI scan revealed impairment in the left lateral sphenoid wall, with CSF present within it. Additionally, there was an empty sella turcica and arachnoid herniation through the sellar diaphragm. This confirmed the diagnosis of a CSF fistula, which was linked to intracranial hypertension and ESS.

Another case involving a rupture in the sphenoidal region was described by Darouassi *et al.* This particular case involved a 49-year-old Arab man who initially received treatment for allergic rhinitis due to his symptoms of CSF rhinorrhea. However, an MRI scan revealed significant abnormalities, including a rupture in the roof of the sphenoid sinus, an empty sella turcica and a pituitary arachnoidocele. During the evaluation of his eye fundus, early papilledema was detected. This

finding suggests the presence of intracranial hypertension as the 'denouement' of this case report (25).

Ammar *et al* reported a case similar to our patient, where a 50-year-old woman experienced recurrent bacterial meningitis, persistent headaches and CSF rhinorrhea for approximately one year. The CT scan revealed a defect in the posterior wall of the right sphenoid sinus and an empty sella turcica. In their review, Schlosser *et al* highlight that an empty sella turcica comes secondary to intracranial hypertension that provokes CSF leakages. They found that, among patients with spontaneous CSF rhinorrhea, 27% had completely empty sellas and 33% partially empty sellas (23).

Cerebrospinal fluid leakage is a potentially fatal medical condition associated with medical emergencies such as meningitis and brain abscesses. Neglected fistulas carry a meningitis risk of 10% to 36.5%, which rises with diagnostic delays (26). Common pathogens include *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*, with less frequent agents including *Neisseria lactamica*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. *Escherichia coli* tends to be more common among patients with impaired immune systems (27). Post-meningitic complications (e.g., hydrocephalus, brain abscesses, neurological deficits) highlight the urgency of prompt diagnosis (28).

Cerebrospinal fluid drainage should be suspected in patients with rhinorrhea, otorrhea or neurological symptoms, particularly after trauma or surgery. Diagnosis starts with collecting nasal discharge, preferably via maneuvers that provoke the leak. Chemical analysis of CSF leak is the cornerstone of the diagnosis. One primary screening method with high sensitivity and specificity is testing for B2-transferrin – a protein produced as a result of neuraminidase activity within the brain that is predominantly found in CSF.

The presence of B2-transferrin in nasal or otologic discharge, analyzed through immunoblotting or immunofixation, is indicative of a CSF leakage and should be conducted for all patients suspected of having CSF rhinorrhea (29, 30). Another protein, called beta-trace protein, can also be detected in abundance in CSF and it is used to identify possible leaks. While this test is fast and cost-effective with high sensitivity, its limited availability in some regions and unsuitability for pa-

tients with bacterial meningitis and renal failure pose challenges to its utilization (31).

Accurate leak localization is crucial for surgical planning. Neuroimaging methods play a vital role in identifying the precise location of CSF drainage, determining possible causes and devising an effective therapeutic strategy. A combination of high-resolution CT scan, CT cisternography, MRI scan and MRI cisternography are employed to confirm the diagnosis of CSF rhinorrhea (5). The initial evaluation of CSF drainage often involves the use of a CT scan as it provides valuable information (32).

In cases where the clinical and radiological findings align, CT cisternography is often unnecessary as it requires a lumbar puncture and can be bothersome for patients (32). However, in patients with multiple bony defects, CT cisternography can be helpful for confirming the location of the leak only when there is an active flow of contrast material during administration. This modality is particularly useful for identifying leaks in the frontal and sphenoid sinuses because these sinus areas act as "containers" that hold the contrast material (29, 33). By utilizing both MR cisternography and HRCT imaging of the skull base, radiologists are able to precisely identify the site of the cerebrospinal fluid leak as well as any associated osseous defects.

On the other hand, MRI cisternography may be advantageous for patients experiencing intermittent leaks or suspected meningoencephaloceles. This imaging technique utilizes heavily T2-weighted images, which enhance the contrast between cerebrospinal fluid and skull base structures. By combining MR cisternography with high-resolution CT imaging of the skull base, healthcare professionals can accurately locate both sites of CSF leakage and any underlying osseous defects.

Once a CSF fistula is detected, appropriate therapeutic intervention should be designed based on the location, pathophysiology and flow volume of the impairment. For low-volume CSF leaks, treatment options may include bed rest, elevating the head position and avoiding activities that increase middle-ear pressures such as Valsalva maneuvers or nose blowing (2, 29). It is important to note that most CSF leaks usually resolve spontaneously within 7 to 10 days. However, for persistent fistulas lasting longer than

10 days there is an exponential increase in the risk of developing meningitis (5).

When conservative measures fail to address a CSF fistula, surgical intervention becomes necessary. There are two main approaches for surgical repair: open craniotomy or endoscopic procedures (2, 29). However, the current consensus favors intranasal endoscopic repair as the preferred method due to its high success rate and lower morbidity, particularly in cases involving the ethmoid roof or sphenoid sinus. In more complex situations where there are intracranial complications involved, an intracranial approach may be warranted (5).

Regardless of the surgical technique used, the recurrence of CSF rhinorrhea is relatively high. Therefore, long-term management and monitoring of patients with CSF rhinorrhea is necessary to ensure the success of the surgical repair and minimize the risk of recurrence (34). Regular follow-up evaluations should include intranasal office endoscopy to assess the integrity of the repair site and identify any signs of recurrent CSF leakage. Patient education and follow-up are crucial components of the management of CSF rhinorrhea. Patients should be educated about the importance of adhering to postoperative care instructions, which may include restrictions on physical activity, avoidance of nose-blowing and sneezing with the mouth closed to prevent increases in intracranial pressure. Patients should also be informed about the signs and symptoms of recurrent CSF rhinorrhea and instructed to seek medical attention if they experience any new or worsening symptoms such as persistent nasal discharge, headaches, or changes in vision. In addition, regular follow-up appointments are necessary to monitor the patient's progress, assess the

integrity of the surgical repair and detect any signs of recurrent CSF leakage.

Limitations of the study

This case report is limited by its single-patient nature, which restricts generalizability. The unavailability of neurosurgical treatment at our institution necessitated referral to another center, resulting in loss of follow-up and limiting our ability to assess long-term outcomes, including surgical repair efficacy and recurrence risk.

CONCLUSIONS

This case underscores the significance of precise diagnosis and localization of CSF leaks. Identifying the underlying cause can be a difficult task. The formation of fistulas on the posterior wall of sphenoid sinus is considered uncommon and rare. Based on our thorough evaluation, we have identified empty sella turcica syndrome as the most likely explanation for the patient's condition. ESS and spontaneous CSF rhinorrhea are often "the two sides of the same coin", as they are pathophysiologically interconnected. In cases of spontaneous CSF leakage, it is imperative to consider the possibility of an empty sella turcica as the underlying cause. To effectively manage CSF rhinorrhea and make informed decisions regarding surgical repair, it is crucial to accurately identify the exact location of the leak site as well as uncover the underlying cause. □

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Informed consent: We undersign, certificate that we have obtained the written consent of the identifiable person in order to present the cases in this scientific paper.

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