Clinical Reasoning:
A 42-year-old man with severe headache, fever, and acute coma

SECTION 1
A 42-year-old man underwent brain MRI at a local health facility for severe headache and was found to have a pituitary adenoma. Two days later, he presented to the emergency department of our hospital with high fever and sudden-onset coma. The patient had a history of intermittent moderate headache in the recent 8 months. No medical history of vascular risk factors was identified.

On examination, his Glasgow Coma Scale score was 4/15, blood pressure was 133/86 mm Hg, and body temperature was 40°C. Blood oxygen saturation was 96% on room air and the respiratory rate was 19 breaths per minute. Neurologic examination revealed neck stiffness. The patient could open his eyes briefly and weakly in response to painful stimuli, with suspected right ptosis. His pupils were equal in diameter, and there was a right relative afferent pupillary defect. His gag reflex was present bilaterally. Spontaneous movements and motor responses to stimuli were absent. His extremities were flaccid and deep tendon reflexes were symmetric. The left Babinski sign was present. Cardiovascular examination was unremarkable. Blood tests revealed remarkable hyponatremia (126 mmol/L) and elevated leukocyte count (12.6 × 10⁹/L).

Questions for consideration:
1. What is the differential diagnosis?
2. What would be the next step to confirm diagnosis?
SECTION 2
In the case of this 42-year-old patient with coma, fever, and neck stiffness, infectious diseases of the nervous system should be considered. Neurologic examination also indicated impairments of cranial nerves II and III and the pyramidal tract. A brain CT and lumbar puncture were performed to determine the causes of these deficits.

The brain CT revealed massive asymmetric hypodensities in both hemispheres, mainly located in the frontal, parietal, and temporal lobes (figure 1). Subarachnoid hemorrhage was excluded after lumbar puncture revealed clear CSF with elevation of protein level (1.06 g/L). Opening pressure, leukocytes, and glucose level were within normal ranges. No red blood cells were detected, and no organisms were found in culture samples. Taking into account the preexisting suprasellar mass and the impairments of cranial nerves II and III, pituitary apoplexy, which is characterized by thunderclap headache, visual deterioration, ophthalmoplegia, signs of meningeal irritation, alteration in consciousness, and hormone dysfunction, became another important consideration. However, the unilateral Babinski sign and brain CT clearly indicated that the lesions were not merely confined to the pituitary gland and its adjacent structures.

Questions for consideration:
1. What additional tests/studies should be considered?
2. What is the association among bilateral cerebral hemisphere lesions, pituitary adenoma, and electrolyte imbalance?
3. What treatment could be given to this patient?
SECTION 3

Another brain MRI was performed, and diffusion-weighted imaging (DWI) revealed high signal conforming to the territories supplied by both anterior cerebral arteries (ACAs) and the right middle cerebral artery (MCA) (figure 2, A–C). The areas of high signal on DWI were smaller than those of radiolucency on CT scan, which suggested that parts of the lesions appearing on initial CT were vasogenic edema rather than cerebral infarction. A pituitary macroadenoma was found to encompass the right internal carotid artery (ICA) in the cavernous sinus. Compared to its isointensity on the initial T1-weighted image, the pituitary adenoma partially turned hyperintense on both T1- and T2-weighted images, indicative of intratumoral hemorrhage (figure 2, E and F). Cranial magnetic resonance angiography disclosed severe narrowing of the distal right ICA and poor visualization of both ACAs, consistent with the diagnosis of an acute massive cerebral infarction in the territory of both ACAs and the right MCA (figure 2D). In the absence of conventional vascular risk factors, the patient’s infarcts were attributed to pituitary apoplexy with resulting ICA compression.

Given the high fever, hyponatremia, and pituitary apoplexy, adrenal insufficiency seemed likely. The patient was therefore treated empirically with IV steroids. Tests of pituitary-related hormones indicated slightly decreased levels of prolactin and testosterone, while the thyroid hormone, growth hormone, insulin-like growth factor I, estrogen, and cortisol were within normal ranges. These results might have been partly affected by steroid treatment.

The patient’s temperature and serum electrolytes normalized soon after treatment and he gradually recovered alertness. Detailed neurologic examination revealed significant vision loss of the right eye with optic nerve atrophy, right ptosis, left hemiplegia, and left Babinski sign. The patient also had significant hypermyotonia on right extremities, which might have been related to the infarction in the left frontal lobe. The patient underwent transsphenoidal tumor removal 1 month after symptom onset. Histologic examinations revealed diffuse necrosis and hemorrhage in the nonfunctional pituitary adenoma. Right ptosis recovered after surgery and left hemiplegia gradually improved via rehabilitation.

Transcranial Doppler sonography was used to monitor the blood flow, showing no flow signal in either ACA and significant dampening of MCA flow, indicative of an arterial steno-occlusive lesion. No restoration was found until surgical intervention took place (figure 3).

Question for consideration:

1. What is the pathophysiologic mechanism of this patient’s presentation?

Figure 2 Brain MRI and magnetic resonance angiography

Diffusion-weighted images reveal restricted diffusion in the bilateral anterior cerebral artery (ACA) and right middle cerebral artery territories (A–C). Magnetic resonance angiography suggests severe narrowing of the right distal internal carotid artery (ICA) and poor visualization of both ACAs (D, arrows). The pituitary macroadenoma was partially hyperintense on T1-weighted images (E), which was indicative of intratumoral hemorrhage, with enhancement of the peritumoral surface (F). The pituitary adenoma extended to the cavernous sinus causing bilateral compression of the intracavernous ICA, worse on the right (E, arrows).
Figure 3 Transcranial Doppler findings before and after surgical removal of the pituitary tumor

(A) Transcranial Doppler sonography before surgery demonstrates severe narrowing of bilateral middle cerebral arteries and anterior cerebral arteries, worse on the right, and increases in mean and peak flow velocities in the bilateral posterior cerebral arteries, which indicates the development of collaterals through posterior communicating arteries. (B) The blood flow of these arteries became normal after surgical intervention. ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery.

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SECTION 4
Pituitary apoplexy is commonly due to intratumoral hemorrhage or hemorrhagic infarction in pituitary adenomas, leading to a sudden volume increase. Pituitary adenomas are prone to autoinfarction or apoplexy even without any trigger because of the local vascular anatomy. Blood supply of the anterior pituitary lobe is provided by portal vessels through the infundibulum. As the perfusion pressure of portal vessels is below normal arterial pressure, the pituitary adenoma is particularly susceptible to even minor increments in intrasellar pressure.1 The most common initial symptom is sudden headache, often associated with rapidly worsening visual field defects, ptosis, or ophthalmoplegia caused by compression of the optic nerve and ocular motor nerves surrounding the gland.2 Meningeal irritation is believed to be caused by blood or chemicals released from the pituitary adenoma. This is also followed in many cases by acute symptoms of hormone deficiency, predominantly adrenal insufficiency.

In addition to the widely known presentations mentioned above, cerebral infarct is a rare complication of pituitary apoplexy. Even more rare, bilateral cerebral infarcts have been reported in only 4 cases previously.3–6 Nonetheless, the risk of cerebral ischemia should always be kept in mind when treating pituitary apoplexy.

Intratumoral hemorrhage and hemorrhagic infarction in pituitary tumors can result in a rapid expansion of the tumor mass, which can cause mechanical compression of the cavernous sinus or suprachinoid portion of the ICA.7,8 However, occlusion of the ICA cannot always be fully explained by mechanical obstruction. For this patient, the pituitary tumor expanded around the terminal portion of the ICA, and blood flow of the ACAs and MCA significantly improved after tumor removal, suggesting a compressive etiology.

Cerebral vasospasm may be another important cause of vascular events. The pathophysiology of vasospasm following pituitary apoplexy remains unknown.7,9 Transdiaphragmatic rupture of the sellar adenoma or extravasation of blood from the hemorrhagic or necrotic adenoma into the subarachnoid space is a likely cause.9 Secretion of potent vasoactive substances by the tumor may also contribute to vasospasm.10 We therefore inferred that, for this patient, both mechanical compression and cerebral vasospasm were likely pathogeneses related to the stroke event.

Early decompression surgery is often advocated for pituitary apoplexy to save visual acuity.8 However, it may be harmful when secondary ischemic stroke occurs, since recanalization of the obstructed ICA and hemodynamic changes may cause hemorrhage into infarct. In this patient, surgical intervention was conducted 1 month after onset, and no postoperative complications occurred. The optimal timing for the surgical removal of the apoplectic tumor complicated by massive cerebral ischemia should be taken into consideration.

AUTHOR CONTRIBUTIONS
Dr. Han and Dr. Zhu initiated this report. Dr. Han wrote the first draft of the manuscript. Dr. Zhu revised the manuscript substantially and approved its final version. Dr. Gao performed all the transcranial Doppler sonography described in this article. Dr. Peng, Dr. Mao, Dr. Cui, and Dr. Xing participated in developing the study concept and analysis/interpretation of data.

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