



Refractory Orthostatic Headache: A Case Report and Literature Review

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Headache is a common problem in patients with cancer undergoing active treatment or in cancer survivors. However, severe orthostatic headache is less common and should be carefully differentiated. Spontaneous intracranial hypotension (SIH) is a rare and often misdiagnosed disorder. Neuroimaging is crucial for diagnosing and monitoring SIH. Awareness of SIH is essential because patients with SIH often suffer from severe impairment of quality of life and psychological distress before receiving a correct diagnosis and treatment. We present a case of a 66-year-old man who had squamous cell carcinoma of the tonsil, stage IV with multiple metastases, and was diagnosed with SIH during the period of palliative treatment.

Key words: Headache, spontaneous intracranial hypotension, cerebrospinal fluid leakage, epidural blood patches, head and neck squamous cell carcinoma

INTRODUCTION

Among cancer patients who need inpatient neurological consultation, 15.4% have headache.¹ In patients with intracranial tumors, the prevalence of headaches was 47.6%.² Other types of headaches in patients with cancer included primary headaches or cancer therapy.

However, abrupt-onset thunderclap headache is rare and can be life-threatening. The common causes of this type of severe headache are reversible cerebral vasoconstriction syndrome and subarachnoid hemorrhage. Other less common causes include infection (intracranial and sinusitis), cerebral venous sinus thrombosis, intracranial vascular disorders (ischemic stroke, intracerebral hemorrhage, and aneurysm), cervical artery dissection, and spontaneous intracranial hypotension (SIH).³

SIH is generally caused by spontaneous cerebrospinal fluid (CSF) leakage. The most common symptom is an orthostatic headache. Vestibulocochlear symptoms (dizziness, tinnitus, and hearing problems), nausea, disequilibrium, posterior neck pain, and cognitive impairment are

common presentations.⁴ Gadolinium-enhanced magnetic resonance imaging (MRI) typically reveals pachymeningeal enhancement, subdural fluid collection, engorged dural venous sinuses, and brain sagging.⁴ If SIH is suspected on brain imaging, nonenhanced MRI of the entire spine is indicated to identify the site of a CSF leakage.⁵ The most common site of leakage is the thoracic spine, followed by the cervical spine and less commonly the lumbar spine.⁶ The initial management consists of conservative treatment, including bed rest, caffeine use, abdominal binder, and oral hydration. When conservative treatment fails, an epidural blood patch (EBP) with autologous blood is used for spinal CSF leaks.⁷

We describe the case of a 66-year-old man who had squamous cell carcinoma of the tonsil, stage IV with multiple metastases, and was diagnosed with SIH during the period of palliative treatment.

CASE REPORT

A 66-year-old man with smoking habit had no history

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of systemic disease. He was diagnosed with squamous cell carcinoma of the tonsil, left, cT2N2cM1, stage IV with multiple lymph nodes, right adrenal gland, bone, liver, and stomach metastases in April 2021. He was started on palliative chemotherapy with cisplatin and fluorouracil since May 2021.

He had a severe headache over the right temporal region since October 2021. The headache precipitated in the upright position and was relieved in the supine position. It showed poor response to analgesics. He denied the presence of dizziness, fever, emesis, and visual symptoms. He also denied any history of radiculopathy symptoms, CSF rhinorrhea, or recent head injury. The neurological examination showed essentially normal findings. Contrast-enhanced brain computerized tomography (CT) revealed no brain metastasis. Gadolinium-enhanced MRI showed no evidence of diffuse pachymeningeal enhancement and brain sagging [Figure 1c-e]. A neurologist was consulted for evaluation, and an intracranial hypotension-related orthostatic headache was suspected. Lumbar puncture examination revealed an opening pressure of 5 cm-H₂O. CSF analyses demonstrated RBC count 2/uL, WBC count 0/uL, PMN 0%, glucose 58 mg/dL, total protein 62 mg/dL, and no cell or organism was found. The MRI myelography image revealed one area of localized fluid collection in the left foraminal epidural space at the T4–T5 level, indicating the presence of a CSF leakage [Figure 1a].

CT-assisted targeted EBP was performed after the diagnosis of SIH in December 2021. The radiologist injected 20cc of blood for an epidural patch. Because the headache was only partially relieved and the symptom recurred several days after the first EBP, we performed CT myelography that revealed a suspected CSF leakage at the T5–T6 level [Figure 1b]. However, we did not repeat the targeted EBP because he was unable to cooperate for this procedure.

The recurrent severe headache was still noted. Contrast-enhanced brain CT disclosed an osteolytic lesion involving the right side of the foramen magnum. Furthermore, he developed poor appetite, severe anemia, and tarry stool during hospitalization. Weeks after the diagnosis of SIH, his clinical condition deteriorated rapidly, and he died due to suffocation.

DISCUSSION

We describe a case of a patient who developed severe orthostatic headache during treatment for his metastatic squamous cell carcinoma. The differential diagnoses of orthostatic headache include traumatic CSF leakage, postural tachycardia syndrome, migraine, benign exertional headache, cerebral venous thrombosis, cervicogenic headache, sinusitis, intracranial neoplasm, and SIH.⁸ SIH is diagnosed using a

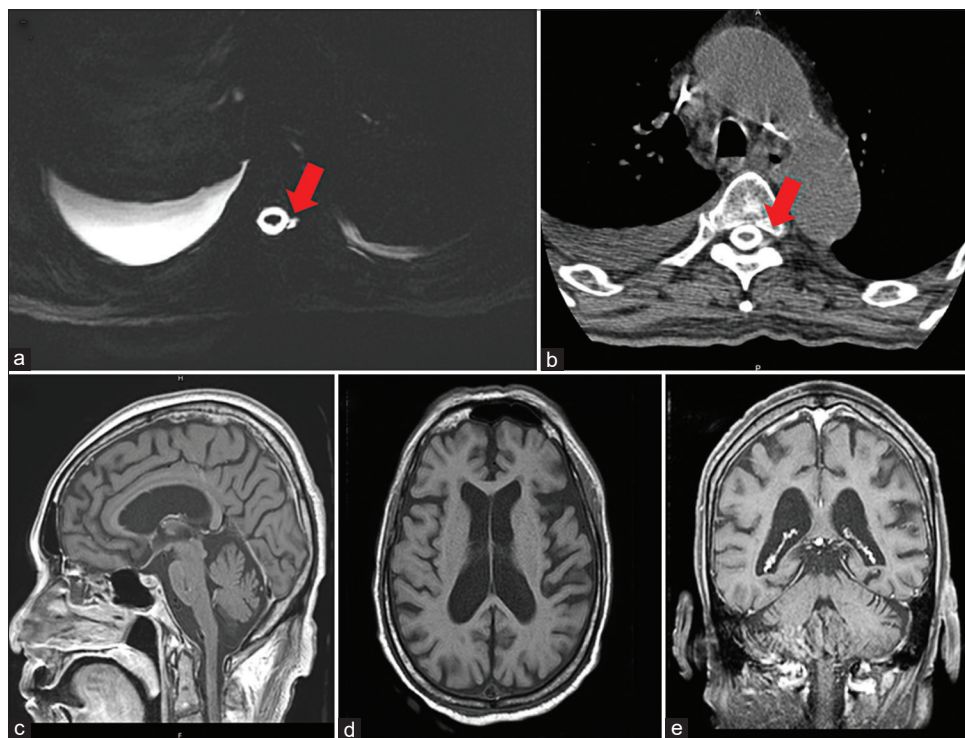


Figure 1: (a) MRI myelography image showed one area of localized fluid collection (red arrow) in the left foraminal epidural space at T4/5. (b) CT myelography showed one area of localized contrast collection in the left foraminal epidural space at T5/6 (red arrow). (c-e) Brain MRI showed no evidence of brain metastasis, pachymeningeal enhancement, subdural fluid collections, and brain sagging. MRI = Magnetic resonance imaging; CT: Computerized tomography

combination of clinical signs and symptoms, images, and CSF pressure measurement. According to the diagnostic criteria of the International Classification of Headache Disorders, third edition, SIH is any headache attributed to low CSF pressure or CSF leakage (no previous procedure or trauma that may cause CSF leakage within 1 month), and its development shows a temporal relationship with low CSF pressure or CSF leakage.⁹ The headache of our patient fulfilled the following diagnostic criteria of SIH: low CSF pressure, evidence of CSF leakage in CT and MRI myelography, and the accompanied symptoms of orthostatic headache. The brain MRI revealed no characteristic findings. In fact, it has been reported that approximately 20% of patients with SIH may have normal findings on brain MRI.⁶

The initial management of SIH comprises conservative treatment, including bed rest, oral hydration, and caffeine use.⁴ However, conservative treatment is unlikely to provide long-term relief of SIH. An EBP is frequently used and is considered the standard treatment after the failure of a conservative approach. The EBP can increase CSF pressure and forms a plug that seals the dural hole to prevent further CSF leakage.⁸ The EBP procedure can be performed in a blinded manner through the lumbar region or by targeting the leakage site under fluoroscopy or CT guidance. Symptomatic relief can be achieved after one or two EBP procedures in most cases.^{6,7} For patients with persistent symptoms after two or three EBP procedures, surgical intervention may be considered when a leakage site is identified.⁸ The response rate of EBP in patients with SIH is variable, ranging from 30% to 90%.^{10–13} Several factors, including higher injected volume, multilevel vertebral injection, and targeted method, are known to be related to better EBP efficacy.^{10,11,13} The symptoms of our patient improved after the EBP procedures; however, the relief was not durable (lasted for 3–4 days after the procedure). The poor response to EBP in our patient may be due to persistent CSF leakage after the EBP procedure.

It is also necessary to consider the secondary causes of the headache, including brain metastases and cerebral venous thrombosis (due to cancer-related hypercoagulability), in patients with cancer. In this context, studies have reported cervicogenic headaches caused by metastasis to cervical lymph nodes adjacent to the superficial cervical plexus and compression of the C3 spinal nerve root by metastatic tumor invasion.^{14,15}

The whole-body bone scan revealed multiple bone metastases and contrast-enhanced brain CT disclosed an osteolytic lesion involving the right side of the foramen magnum. The osteolytic lesion involving the right side of the foramen magnum was not seen in the whole-body bone scan or PET scan initially but was found in the brain CT. The new lesion may be due to disease progression. However, such lesions will not lead to the symptoms of severe headaches such

as SIH. On the other hand, the CSF leakage sites seen in the MR or CT myelography were not compatible with the metastatic sites. We believed that the spontaneous CSF leakage was due to an unknown cause where occult metastases which were not detected in the current image studies could not be excluded.

There have been reports of patients with cancer with SIH which were provided in Supplementary Information, and we have summarized the details regarding clinical symptoms, neuroimaging, treatment, and outcomes in Supplementary Information 1-Table 1: Case Presentation. The clinical symptoms and brain imaging findings were typical for SIH. Most patients received the EBP procedure in addition to conservative treatment with fair outcomes. However, there were three fatal cases, including our patient, due to difficulty in repeating the EBP procedure. The prognosis of SIH in patients with cancer depends on early recognition and appropriate management.

CONCLUSION

SIH must be considered in all patients with cancer with new-onset headaches despite the lack of typical findings on brain MRI. Prompt spinal imaging and early intervention, including conservative treatment and EBP, are indicated to relieve symptoms and improve the quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

The data that support the findings of this study are available from the corresponding author, PY Chang, upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY INFORMATION 1: TABLE 1

Table 1: Case Presentation

Case	Presentation	Symptoms	Brain MRI finding	Spine images	Treatment	Outcome	Reference
1	49/M, OPSCC, stage not mentioned, but at least stage III	PH Coma	BPE, SFC, DD	Spinal MRI and technetium radionuclide scan did not reveal any CSF leaks	Conservative treatment Blind EBP*2	Well recovery	[1]
2	64/M, NHL, Ann Arbor stage II	ΔMS Hemiparesis Mydriasis	PE, EBC, SFC, DD	Spinal MRI did not find any nerve root abnormality	Conservative treatment Blind EBP*2	Poor response; expired*	[2]
3	58/F, IDC of breast, stage IIIC	PH N/V Ptosis Balance troubles	PE, SFC	MN	Conservative treatment Discontinue capecitabine 16 mg dexamethasone	Well recovery	[3]
4	64/F, clival chordoma, stage not mentioned	ΔMS PH N/V	EBC, EDS, DD	MN	Conservative treatment Surgical repair	Well recovery	[4]
5	59/F, RCC, stage IVB	ΔMS	BPE, EDS, SFC, DD	Spine CT myelography revealed no contrast extravasation	Conservative treatment Target EBP*1	Well recovery	[4]
6	32/M, acute T-cell lymphoma in complete remission	PHΔMS	EBC, DD	Spine MRI failed to localize a site of CSF leakage	Conservative treatment Target EBP*1	Well recovery	[4]
7	58/F, IDC of breast, stage IIB	PH Diplopia	N	Spine MR myelography found an increased anterior epidural space in C1-C2 level with enhancement	Conservative treatment Stop tamoxifen	Well recovery	[5]
8	60/F, CUP	PH Dizziness N/V	BPE	Spine MR myelography showed CSF accumulation at the level of C5-6	Conservative treatment Target EBP*1	Poor response; expired*	[6]
9	64/M, SqCC of lung, stage IB	PH	BPE, SFC	The spinal MRI showed no CSF leak site and no meningeal carcinomatosis	Conservative treatment	Well recovery	[7]
10	65/F, AdenoCA of lung, stage not mentioned	PH Ear fullness	BPE, SFC	Spine MRI found unremarkable findings	Conservative treatment Target EBP*2	Well recovery	[8]
11	66/M, SqCC of tonsil, stage IVC	PH	N	Spine MR myelography showed localized fluid collection at T4-T5 level	Conservative treatment Target EBP*1	Poor response; expired	[Our case]

Case 2 expired due to lung infection, and case 8 expired due to respiratory failure.

Abbreviation: SqCC=squamous cell carcinoma; PH=postural headache; BPE=brain pachymeningeal enhancement; SFC=subdural fluid collection; DD=downward displacement of the brain; Conservative treatment=Bed rest + Oral caffeine + Hydration; EBP=Epidural blood patch; NHL=nonHodgkin lymphoma; ΔMS=Mental status change (but not coma); PGE=pituitary gland enlargement; EBC=effacement of basilar cisterns; IDC=invasive ductal carcinoma; N/V=nausea/vomiting; MN=Not mentioned; EDS=engorged dural sinuses; RCC=renal cell carcinoma; N=No SIH-related image finding; CUP=carcinoma of unknown primary; AdenoCA=adenocarcinoma.

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