Probable cavernous sinus-adjacent meningeal metastasis from esophageal squamous cell carcinoma: A case report

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Abstract. Meningeal dissemination from esophageal squamous cell carcinoma (ESCC) is exceptionally rare, and cavernous sinus-adjacent involvement has been only sparsely described. The present study reports the case of a 59-year-old man with controlled extracranial ESCC who presented with acute oculomotor and trochlear nerve palsies shortly after severe acute respiratory syndrome coronavirus 2 infection. Although the symptoms were initially attributed to post-viral neuropathy, contrast-enhanced magnetic resonance imaging demonstrated multifocal nodular meningeal enhancement and irregular dural thickening adjacent to the cavernous sinus, findings highly suggestive of meningeal metastasis. Cerebrospinal fluid examination and biopsy of the meningeal lesion were not performed; therefore, the diagnosis remained as radiologically supported probable meningeal metastasis from ESCC, and the exact pachymeningeal or leptomeningeal compartment could not be confirsmed. The progression occurred 2 months after resection of a solitary brain metastasis despite sustained extracranial control. This case illustrates sequential parenchymal and probable meningeal central nervous system progression and highlights the risk of anchoring bias when a concurrent viral infection provides an apparently plausible alternative explanation. New focal cranial neuropathies in patients with cancer warrant urgent contrast-enhanced neuroimaging.

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Introduction

Central nervous system (CNS) dissemination is uncommon in esophageal squamous cell carcinoma (ESCC). In two retrospective institutional cohorts, brain metastases were identified in 15 of 4,494 (0.33%) and 66 of 19,225 (0.34%) patients with ESCC, respectively (1,2). Meningeal involvement from esophageal cancer is rarer still; the largest dedicated case series included only seven patients, and ESCC-specific evidence remains largely limited to isolated reports (3-6). Cavernous sinus-adjacent meningeal involvement therefore represents an exceptionally unusual clinical presentation; its rarity reflects an uncommon metastatic pattern requiring tumor spread to the skull-base meningeal or dural compartment rather than to the more typical parenchymal sites. As lesions in this compact neurovascular region may present with ocular motor cranial neuropathies, the initial diagnostic challenge is to distinguish metastatic disease from other neoplastic, vascular, inflammatory and infectious disorders (7,8).

This diagnostic challenge is amplified when a recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection provides an apparently plausible competing explanation. Cranial neuropathies, including oculomotor nerve palsy and ophthalmoplegia, have been reported in temporal association with SARS-CoV-2 infection (9-11). In patients with cancer, however, temporal association alone should not defer evaluation for a structural lesion. The present study reports the case of a patient with ESCC who developed oculomotor and trochlear nerve palsies shortly after SARS-CoV-2 infection, with contrast-enhanced magnetic resonance imaging (MRI) findings highly suggestive of cavernous sinus-adjacent meningeal metastasis despite stable extracranial disease. This case is presented in accordance with the CARE guidelines (12).

Case report

Patient information. A 59-year-old man with a history of hypertension and type 2 diabetes mellitus developed progressive dysphagia of unclear cause in April 2021 and presented to the People's Hospital of Qingbaijiang District (Chengdu, China) in July 2021. The patient had a history of smoking and alcohol consumption for >40 years, with a

smoking index of 800 and daily alcohol intake of ~50 ml of Chinese liquor (Baijiu).

Initial diagnosis and treatment. At that hospital, endoscopy revealed an ulcerative lesion in the distal esophagus (35-42 cm from the incisors), involving three-quarters of the lumen. Endoscopic biopsy revealed irregular nests and cords of atypical squamous epithelial cells infiltrating the stroma, with nuclear pleomorphism, eosinophilic cytoplasm and focal keratinization, supporting the diagnosis of moderately differentiated squamous cell carcinoma (Fig. S1). Subsequently, baseline contrast-enhanced chest computed tomography (CT) demonstrated thickening of the distal esophageal wall (Fig. S2A). According to the contemporaneous 18F-fluorodeoxyglucose (FDG) positron emission tomography/CT report from The General Hospital of Western Theater Command of the Chinese People's Liberation Army (Chengdu, China), the esophageal lesion showed notable FDG uptake and multiple mediastinal lymph node metastases, with no evidence of distant organ involvement. As an endoscopic ultrasound was not performed, the precise T stage could not be determined. Following a multidisciplinary team (MDT) evaluation, including assessment by a thoracic surgeon, the patient was deemed unsuitable for curative resection due to the extent of nodal involvement.

From July to September 2021, the patient received three cycles of systemic chemotherapy consisting of nab-paclitaxel (300 mg intravenously on day 1) and cisplatin (30 mg intravenously on days 1-3) administered every 3 weeks. A follow-up contrast-enhanced chest CT in September 2021 was assessed as stable disease (Fig. S2B). Following an MDT evaluation, surgical resection was deemed unfeasible. Although concurrent chemoradiotherapy was initially planned, the regimen was modified to definitive intensity-modulated radiotherapy (IMRT) due to patient intolerance. Radiotherapy was delivered between September and November 2021, with a total dose of 54.0 Gy administered to the clinical target volume (CTV) in 30 fractions (1.8 Gy/fraction). The patient subsequently completed the fourth and fifth cycles of chemotherapy in December 2021 and started maintenance therapy with oral tegafur (40 mg twice daily) in January 2022. A follow-up chest CT in February 2022 demonstrated a partial response (PR) (Fig. S2C). During the fourth and fifth cycles of chemotherapy, the patient developed grade 2 neutropenia according to the Common Terminology Criteria for Adverse Events, version 5.0 (13), which resolved following subcutaneous administration of recombinant human granulocyte colony-stimulating factor at 150 μg once daily for 3 consecutive days. The patient remained progression-free until September 2022.

Development of parenchymal brain metastasis. In September 2022, the patient developed acute dysarthria and left-sided weakness (muscle strength graded as 3/5), accompanied by dizziness and a headache, but without nausea or vomiting. Emergency brain MRI revealed a heterogeneously enhancing mass in the right frontotemporal lobe (~4.9x5.7 cm) with extensive surrounding edema (Fig. 1A). In late September 2022, the patient underwent resection of a deep supratentorial tumor with decompressive craniectomy. Postoperative histopathological examination demonstrated moderately differentiated squamous cell carcinoma infiltrating the cerebral parenchyma. Immunohistochemical staining was positive for CK5/6, CK8/18 and p63, focally positive for vimentin, and negative for CK7, CK20, GFAP, S-100 and villin. In conjunction with the patient's known primary ESCC, these morphological and immunohistochemical findings supported the diagnosis of metastatic ESCC (Fig. 2).

Histopathological and immunohistochemical analysis. The resected brain tumor specimen was fixed in 4% neutral-buffered formalin at room temperature for 24-48 h, embedded in paraffin and sectioned at a thickness of 4 μm. Hematoxylin and eosin (H&E) staining was performed at room temperature; sections were stained with hematoxylin for 5-7 min, followed by eosin for 1-2 min.

For immunohistochemical analysis, 4-μm-thick paraffin-embedded sections of the resected brain tumor specimen were deparaffinized and rehydrated. Heat-induced antigen retrieval was performed using citrate buffer (pH 6.0) at 95-100˚C for 20 min. Staining was performed using a Titan S automated immunohistochemistry system (Fuzhou Maixin Biotechnology Development Co., Ltd.). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 15 min at room temperature, and non-specific binding was blocked using 5% normal mouse/rabbit serum (Fuzhou Maixin Biotechnology Development Co., Ltd.) for 30 min at room temperature.

The sections were incubated overnight at 4˚C with primary antibodies against CK5/6 (dilution, 1:100; cat. no. MAB-0744), CK8/18 (dilution, 1:100; cat. no. MAB-1002), p63 (dilution, 1:100; cat. no. MAB-0694), vimentin (dilution, 1:100; cat. no. MAB-0735), CK7 (dilution, 1:100; cat. no. MAB-0828), CK20 (dilution, 1:100; cat. no. MAB-0834), GFAP (dilution, 1:100; cat. no. MAB-0582), S-100 protein (dilution, 1:100; cat. no. MAB-0585) and villin (dilution, 1:100; cat. no. RMA-1090) (all from Fuzhou Maixin Biotechnology Development Co., Ltd.).

Following washing, sections were incubated with the appropriate ready-to-use HRP-polymer anti-mouse or anti-rabbit immunohistochemistry detection reagent (cat. nos. KIT-5002 and KIT-5005, respectively; Fuzhou Maixin Biotechnology Development Co., Ltd.) for 1 h at room temperature. Signal detection was performed using 3,3'-diaminobenzidine (DAB; cat. no. TT-0805; Fuzhou Maixin Biotechnology Development Co., Ltd.), and the sections were counterstained with hematoxylin for 1-2 min at room temperature. Positive and negative controls were run concurrently and exhibited appropriate staining. All slides were examined and imaged using an Olympus BX43 light microscope (Olympus Corporation) at a magnification of x100 (scale bar, 100 μm).

Postoperatively, the patient received IMRT to the resection cavity from late October to mid-November 2022 (planning gross tumor volume, 5,400 cGy; planning CTV, 4,500 cGy; 18 fractions). This was followed by maintenance immunotherapy with camrelizumab (200 mg intravenously every 3 weeks) in October, November and early December 2022. Follow-up MRI in December 2022 demonstrated good local control of the resected right frontotemporal metastasis (Fig. 1B). At the onset of diplopia, right ptosis, right pupillary dilation and restricted right eye movement in January

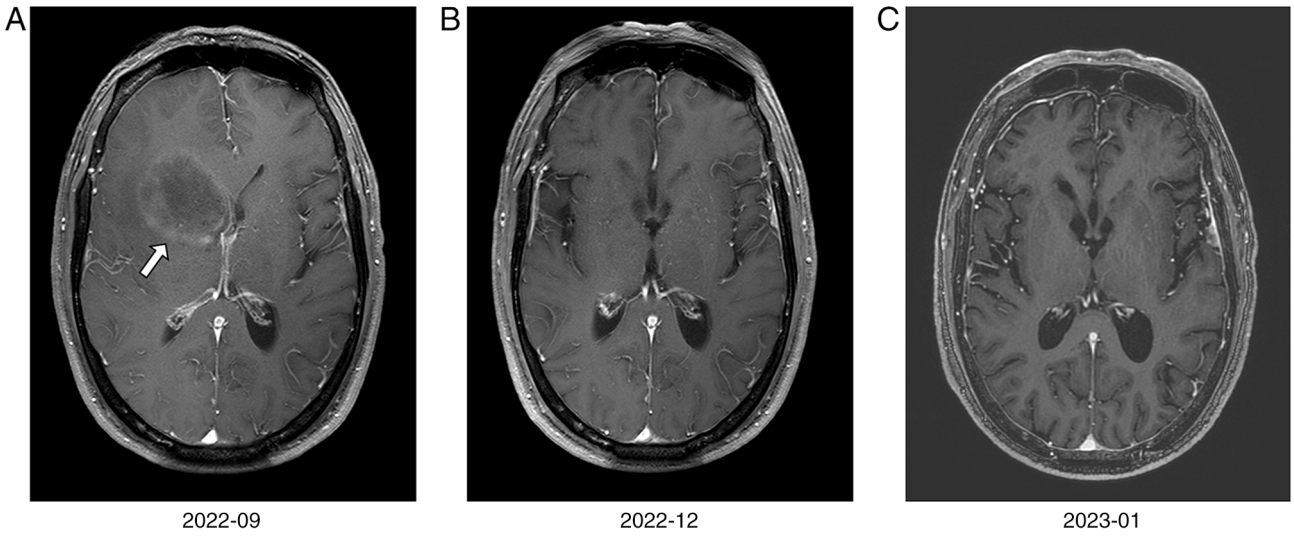

Figure 1. Serial brain MRI of the right frontotemporal parenchymal metastasis. (A) Axial T1-weighted post-contrast image from September 2022 demonstrating a heterogeneously enhancing mass in the right frontotemporal lobe (white arrowhead). (B) Follow-up MRI 2 months after resection (December 2022) showing the resection cavity with no evidence of local recurrence. (C) MRI after the onset of ocular symptoms (January 2023) confirming continued local control at the primary resection site. MRI, magnetic resonance imaging.

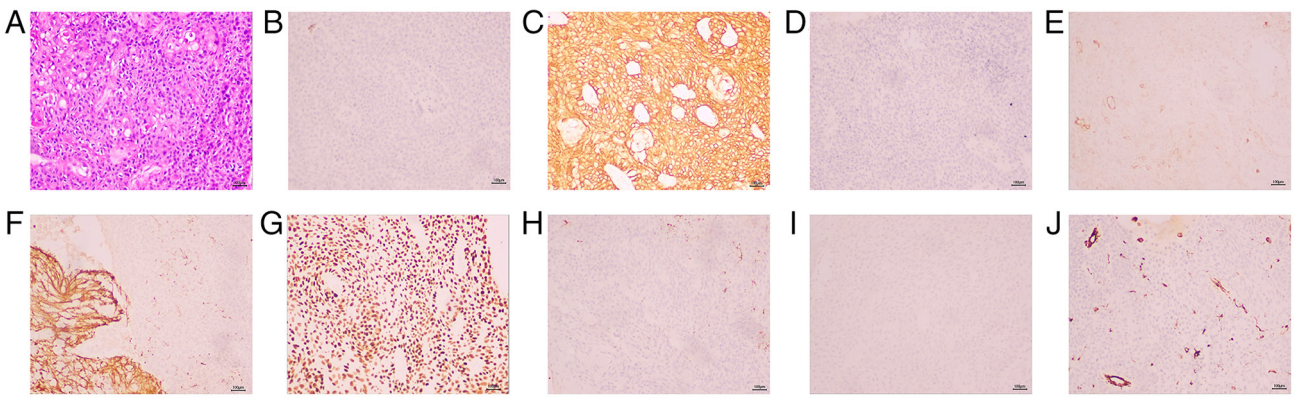

Figure 2. Histopathology of the resected parenchymal brain metastasis. (A) Hematoxylin and eosin staining showing moderately differentiated squamous cell carcinoma infiltrating the cerebral parenchyma. (B) Negative immunohistochemical staining for CK20. (C) Positive immunohistochemical staining for CK5/6. (D) Negative immunohistochemical staining for CK7. (E) Positive immunohistochemical staining for CK8/18. (F) Negative immunohistochemical staining for GFAP. (G) Positive immunohistochemical staining for p63. (H) Negative immunohistochemical staining for S-100 protein. (I) Negative immunohistochemical staining for villin. (J) Focally positive immunohistochemical staining for vimentin. These findings apply only to the resected parenchymal metastasis and do not histologically confirm the later meningeal lesions. Original magnification, x100; scale bar, 100 μm.

2023, repeat MRI confirmed that the resected frontotemporal lesion remained stable, with no evidence of local recurrence (Fig. 1C).

SARS-CoV-2 infection and neurological deterioration. In January 2023, the patient developed a high fever (maximum temperature 39.1˚C) and cough. A nucleic acid test for SARS-CoV-2 was positive. Following the initial presentation, the patient developed diplopia, right ptosis, right pupillary dilation and limited right eye movement, including impaired adduction, elevation and depression (Fig. 3), consistent with oculomotor nerve palsy with trochlear nerve involvement. The patient reported no nasal congestion, runny nose, facial pain or other sinus symptoms. No other focal neurological symptoms or signs were observed at that time.

Due to local pandemic restrictions, an initial telemedicine consultation suspected SARS-CoV-2-associated cranial neuropathy, and urgent neuroimaging was deferred. However, ~1 week later, contrast-enhanced brain MRI revealed multiple scattered nodules and patchy areas of prominent enhancement in the meningeal regions of the bilateral temporal and parieto-occipital lobes, with right-sided predominance. Irregular thickening and marked enhancement of the meninges adjacent to the cavernous sinus were also present (Fig. 4). The patient declined to undergo a lumbar puncture for cerebrospinal fluid (CSF) examination. Considering the prior histologically confirmed parenchymal brain metastasis, the rapid development of multifocal nodular meningeal enhancement and the focal cavernous sinus-adjacent dural thickening, a radiologically supported diagnosis of probable meningeal metastasis from ESCC was made, corresponding to stage IVB according to the eighth edition of the American Joint Committee on Cancer staging system (14). Since neither CSF cytology nor biopsy of the meningeal lesion was available,

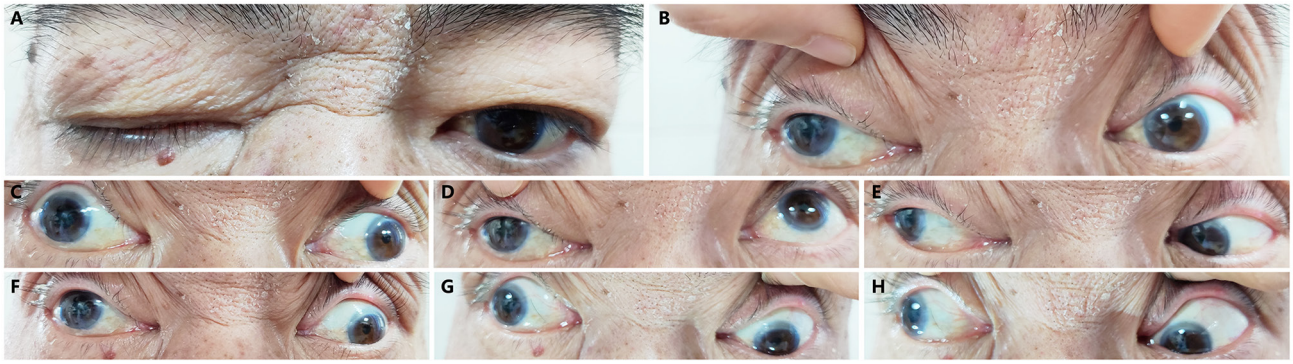

Figure 3. Ocular motility examination after symptom onset. Extraocular movements in cardinal positions of gaze show severe limitation of adduction, supraduction and infraduction of the right eye, consistent with right oculomotor nerve palsy with trochlear nerve involvement. (A) Right ptosis. (B) Primary position. (C) Left gaze. (D) Up gaze. (E) Right gaze. (F) Left-down gaze. (G) Down gaze. (H) Right-down gaze.

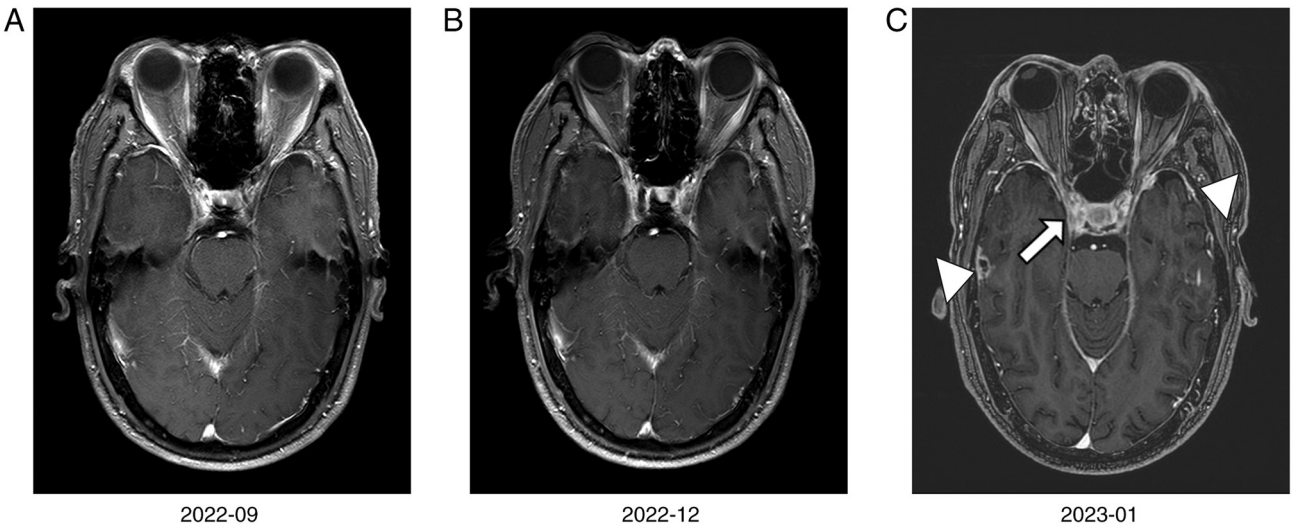

Figure 4. Serial contrast-enhanced T1-weighted brain magnetic resonance imaging demonstrating the evolution of radiologically suspected meningeal disease. (A) September 2022: No abnormal meningeal thickening or enhancement is observed in the cavernous sinus region. (B) December 2022: The cavernous sinus region remains without definite meningeal thickening. (C) January 2023: Multifocal nodular and patchy meningeal enhancement is observed in the bilateral temporal and parieto-occipital regions, with right-sided predominance (white arrowheads). Irregular thickening and marked enhancement of the meninges adjacent to the cavernous sinus are indicated by the white arrow.

metastatic involvement was not pathologically confirmed and the precise distribution between the pachymeningeal and leptomeningeal compartments could not be established. At that time, the primary esophageal tumor and regional lymph nodes remained well controlled.

Therapeutic intervention and outcome. Following the radiologically supported diagnosis of probable meningeal metastasis, immunotherapy was discontinued. In January 2023, the patient started one 21-day cycle of chemotherapy with irinotecan (200 mg intravenously on day 1) and S-1 (tegafur/gimeracil/oteracil; 40 mg twice daily on days 1-10). Whole-brain radiotherapy (WBRT) was initiated 3 days later but was terminated early due to clinical deterioration and intolerance; 15 Gy in 5 fractions was delivered from a planned 30 Gy in 10 fractions. Ondansetron (8 mg by intravenous infusion) was administered once before chemotherapy as antiemetic prophylaxis. Despite prophylactic ondansetron, nausea/vomiting occurred during chemotherapy. Grade 3 myelosuppression was managed with recombinant human granulocyte colony-stimulating factor at 300 μg subcutaneously once daily for 3 consecutive days.

At the family's request, the patient was discharged in mid-January 2023. Subsequent telephone follow-up indicated continued clinical deterioration, and the patient succumbed in March 2023, ~2 months after the radiological identification of probable meningeal metastasis.

To facilitate understanding, the CARE-guided workflow and the key management milestones of this case are summarized in Fig. 5.

Discussion

The present case is notable due to an uncommon sequential CNS metastatic course in ESCC: A histologically confirmed parenchymal brain metastasis was followed within 2 months by radiologically supported probable meningeal disease with cavernous sinus-adjacent dural involvement, while

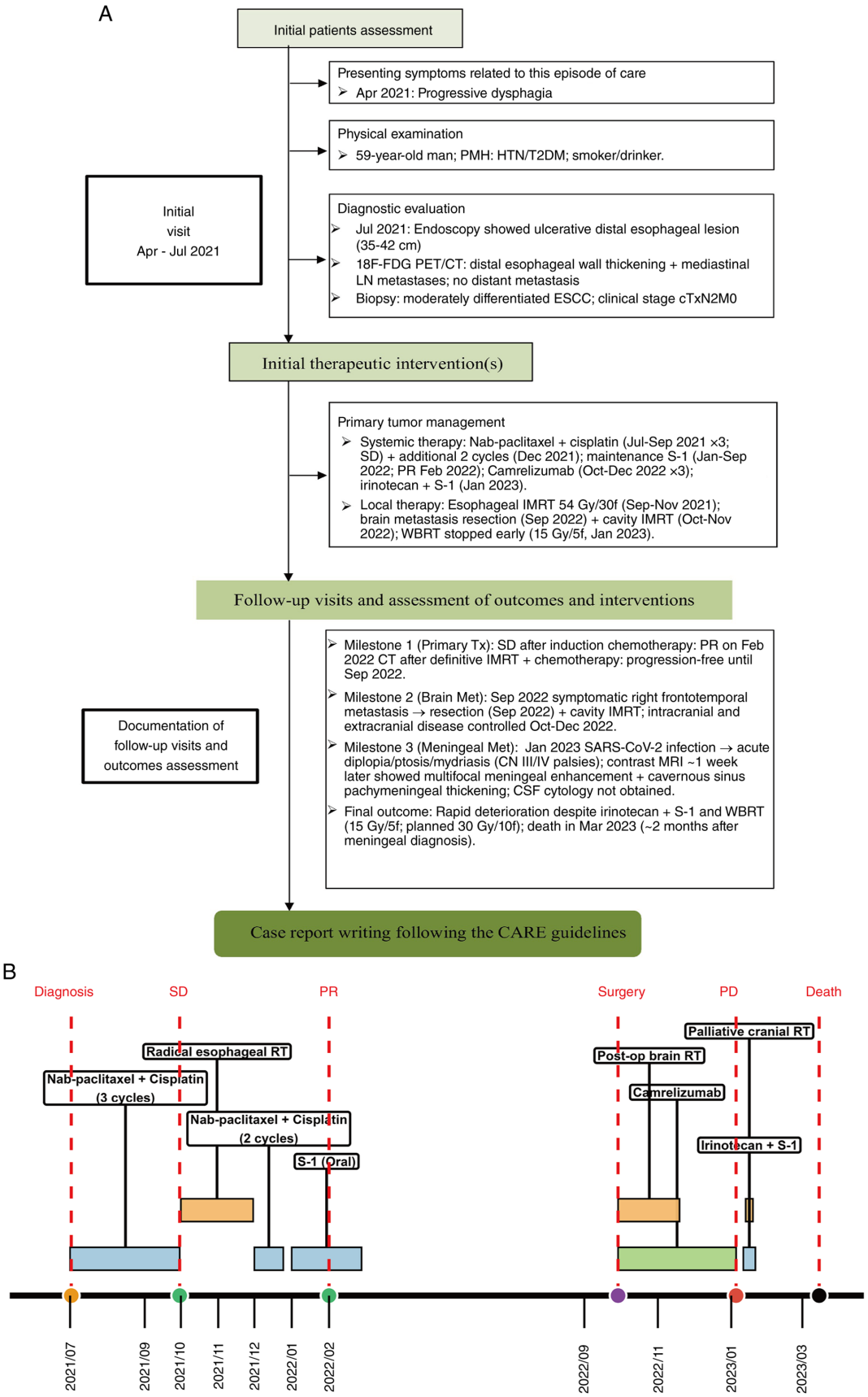

Figure 5. CARE-guided workflow and clinical timeline of the present case. (A) Flow diagram summarizing patient presentation, diagnostic evaluation, treatment and follow-up in accordance with the CARE guidelines. (B) Timeline of the clinical course (April 2021-March 2023) showing key milestones and sequential multimodal management for ESCC. Treatment regimens and local therapies are annotated. Colored bars indicate treatment periods. Vertical dashed lines mark major events and response assessments (diagnosis, SD, PR, surgery, PD and death). ESCC, esophageal squamous cell carcinoma; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging; IMRT, intensity-modulated radiotherapy; WBRT, whole-brain radiotherapy; CSF, cerebrospinal fluid; LN, lymph node; S-1, tegafur/gimeracil/oteracil; SD, stable disease; PR, partial response; PD, progressive disease; PMH, past medical history; HTN, hypertension; T2DM, type 2 diabetes mellitus.

the primary esophageal lesion and regional lymph nodes remained controlled. The oculomotor and trochlear nerve palsies provided an important localizing clue, whereas the recent SARS-CoV-2 infection offered a plausible competing explanation and increased the risk of anchoring bias.

The temporal association with SARS-CoV-2 infection should be regarded as a diagnostic confounder rather than evidence of causation. Neurological and ocular manifestations associated with SARS-CoV-2 infection are heterogeneous and derive largely from observational reports and small case series (10,11,15,16). Although transient lymphopenia and altered T-cell function have been described during acute infection (17,18), these population-level observations do not establish that SARS-CoV-2 promoted CNS progression in this patient. In a patient with cancer, persistent or progressive focal deficits, particularly pupil-involving oculomotor palsy, should prompt urgent in-person assessment and contrast-enhanced MRI to exclude compressive, infiltrative or vascular disease (19).

In the present patient, neuroanatomical localization was central to narrowing the differential diagnosis. The combination of right-sided ptosis, mydriasis, impaired adduction, elevation and depression, and vertical diplopia was consistent with involvement of cranial nerves III and IV and localized the lesion to the cavernous sinus-superior orbital fissure region. Cranial nerves III and IV course within the lateral wall of the cavernous sinus, whereas cranial nerve VI travels more medially adjacent to the internal carotid artery. This anatomical arrangement provides a plausible, although unconfirmed, explanation for the relative preservation of cranial nerve VI if the disease initially involves the lateral wall (20-22). Proptosis and visual impairment, which may occur when cavernous sinus disease extends anteriorly into the superior orbital fissure or orbital apex (7), were absent, and MRI showed no discrete orbital apex lesion. Instead, the cavernous sinus-adjacent dural enhancement provided a plausible structural correlate for the ocular motor deficits. Comparable manifestations, including ptosis, diplopia and ophthalmoplegia, have been described in cavernous sinus metastases from head and neck squamous cell carcinoma, supporting the clinical plausibility of this localization across squamous malignancies, although these observations do not constitute direct evidence for ESCC (23).

General diagnostic frameworks for multiple intracranial lesions emphasize integration of the clinical context, lesion distribution and imaging characteristics rather than reliance on a single sign (24,25). In the present patient, neoplastic alternatives included meningioma, other sellar or parasellar tumors, perineural tumor spread and lymphoma; these were considered less likely as there was no discrete sellar, parasellar or nerve-centered mass, with the lesions developing rapidly as multifocal nodular meningeal enhancement in a patient with recently confirmed ESCC brain metastasis. Primary CNS diffuse large B-cell lymphoma and primary dural marginal zone lymphoma remain relevant imaging mimics (26,27), but the oncological history and short-interval pattern in the present patient favored metastatic disease. Tolosa-Hunt syndrome and granulomatous pachymeningitis were less consistent with the absence of painful ophthalmoplegia and the presence of multifocal nodular rather than smooth diffuse meningeal enhancement. Invasive fungal sinusitis was less likely, as neither sinonasal symptoms nor destructive sinonasal changes were present, although infection cannot be excluded by symptoms alone. Internal carotid artery aneurysm, carotid-cavernous fistula and cavernous sinus thrombosis were also considered less likely, as MRI showed no aneurysmal dilatation, abnormal flow-related signal or cavernous sinus filling defect, and there was no acute orbital congestion or proptosis (7).

Taken together, the previous histologically confirmed ESCC brain metastasis, short-interval progression, multifocal nodular enhancement and focal dural thickening favored metastatic involvement in the present study. However, MRI cannot establish histological identity, and neither CSF cytology nor biopsy of the meningeal lesion was available. The diagnosis should therefore remain radiologically supported and probable; the cavernous sinus-adjacent thickening suggests pachymeningeal involvement, whereas the additional nodular enhancement leaves concomitant leptomeningeal disease as a possibility (28,29).

Looking beyond the diagnosis, the lesion distribution raises the question of the metastatic route followed. Dural metastases may arise through systemic arterial hematogenous dissemination, valveless vertebral venous channels such as Batson's plexus, dural vascular spread or direct extension from adjacent skull disease; leptomeningeal dissemination may also result from hematogenous seeding, perineural spread or release of tumor cells from parenchymal metastases into CSF spaces (30-32). In the present patient, the new lesion was remote from the resection cavity and surgical corridor, with no contiguous or adjacent skull lesion on serial MRI. Direct operative-tract seeding and skull-to-dura extension were therefore less likely, leaving hematogenous or CSF-mediated dissemination plausible but unproven; postoperative pachymeningeal or nodular meningeal seeding has been described after resection of brain metastases in other primary tumors, providing a relevant but non-causal analogy (33).

Although larger retrospective and surgical series characterize parenchymal brain metastases from ESCC or esophageal cancer (1,2,34), directly comparable ESCC meningeal or dural reports are scarce. Komatsu *et al* (6) described the case of a 72-year-old man whose hearing impairment, blurred vision, facial numbness and gait disturbance led to the diagnosis of leptomeningeal carcinomatosis, which was supported by MRI and CSF cytology. Chen and Huang (5) reported the case of a 62-year-old man with headache, diplopia and severe hearing impairment associated with diffuse pachymeningeal thickening and skull metastases ~4 months after initial treatment; WBRT produced neurological and radiological improvement, but the patient subsequently died with progressive systemic disease. In the 7-patient series by Lukas *et al* (3), the interval from primary diagnosis to meningeal disease ranged from 5 months to 3 years and 11 weeks, and survival time after meningeal diagnosis was 2.5-16 weeks. In a recent gastroesophageal cohort, all leptomeningeal cases were adenocarcinomas, the median interval from primary diagnosis was 4.9 months and the median survival time was 2.8 months with WBRT vs. 0.7 months with best supportive care (35). The present case differs in its histological subtype and sequence: Probable meningeal progression occurred ~18 months after ESCC diagnosis but only 2 months after

Table I. Comparison of selected reports of meningeal or dural metastasis from esophageal or gastroesophageal carcinoma with the present case.

First author, year	Pattern and histology of CNS involvement	Presenting symptoms	Interval from primary diagnosis	Treatment	Survival after CNS diagnosis	(Refs.)
Komatsu *et al*, 2014	Leptomeningeal ESCC (n=1)	Hearing loss; blurred vision; facial numbness; gait disturbance	Synchronous with primary diagnosis	NR	NR	(6)
Chen and Huang, 2014	Dural/skull ESCC (n=1)	Headache; diplopia; hearing loss	~4 months after initial treatment	WBRT 30 Gy/10 fractions + chemotherapy	NR; died with systemic progression	(5)
Lukas *et al*, 2015	Leptomeningeal carcinomatosis (n=7 esophageal cancer cases; adenocarcinoma was the predominant histology)	Variable neurological presentations	5 months to 3 years and 11 weeks	WBRT initiated in 4 patients (completed in 2); the longest-surviving patient received intrathecal topotecan plus oral temozolomide	2.5-16 weeks after diagnosis of leptomeningeal involvement	(3)
Megid *et al*, 2024	Leptomeningeal (n=20 gastroesophageal adenocarcinoma cases)	Neurological symptoms reported at cohort level	Median, 4.9 months	WBRT (n=12) or best supportive care (n=7)	Median 2.8 months with WBRT; 0.7 months with supportive care	(35)
Present case	Cavernous sinus-adjacent probable meningeal ESCC (n=1)	Ptosis; diplopia; mydriasis; cranial nerve III/IV palsies	~18 months after ESCC diagnosis; 2 months after brain metastasis resection	Irinotecan + S-1; incomplete WBRT 15 Gy/5 fractions	~2 months	

CNS, central nervous system; ESCC, esophageal squamous cell carcinoma; NR, not reported; S-1, tegafur/gimeracil/oteracil; WBRT, whole-brain radiotherapy.

resection of a parenchymal brain metastasis, with extracranial disease still controlled and predominant cranial nerve III and IV palsies. The presenting symptoms, interval from ESCC diagnosis, treatment and survival of the directly comparable ESCC reports and the present case are summarized in Table I.

A further notable feature of the present case was CNS progression despite extracranial control, consistent with systemic-CNS dissociation or CNS sanctuary progression. Differences in drug exposure across the blood-brain, blood-tumor and blood-CSF interfaces, together with compartment-specific immune microenvironments, may contribute to discordant disease control (29,36-38). ESCORT-1st was a randomized, double-blind, placebo-controlled, phase III trial in previously untreated patients with advanced or metastatic ESCC that compared camrelizumab plus paclitaxel and cisplatin with placebo plus paclitaxel and cisplatin. The trial demonstrated an overall survival benefit with camrelizumab plus chemotherapy but excluded patients with CNS metastases (39). KEYNOTE-590 was a randomized, double-blind, placebo-controlled, phase III trial in previously untreated patients with locally advanced unresectable or metastatic esophageal carcinoma or Siewert type I gastroesophageal junction adenocarcinoma that compared pembrolizumab plus cisplatin and 5-fluorouracil with placebo plus cisplatin and 5-fluorouracil; patients with known active CNS metastases and/or carcinomatous meningitis were excluded (40). CheckMate 648 was a global, randomized, open-label, phase III trial in previously untreated patients with unresectable advanced, recurrent or metastatic ESCC that compared nivolumab plus chemotherapy, nivolumab plus ipilimumab and chemotherapy alone; patients with symptomatic brain metastases were excluded (41). Consequently, the intracranial efficacy of immune checkpoint blockade in ESCC remains uncertain and is informed mainly by extrapolation from systemic trials and isolated clinical reports, including a reported complete response of an asymptomatic solitary brain metastasis to toripalimab in a single patient (42). A small phase II study of pembrolizumab in leptomeningeal carcinomatosis from solid tumors reported promising activity, although no patients with ESCC were included (43). Camrelizumab is a humanized monoclonal antibody directed against programmed cell death protein 1 (PD-1); therefore, CNS progression during camrelizumab treatment in this single patient cannot be interpreted as evidence of inadequate CNS drug exposure or a lack of intracranial activity of PD-1 blockade.

Management of meningeal metastatic disease from solid tumors is individualized and generally palliative, with treatment selection guided by neurological status, performance status, disease distribution, CSF flow, extracranial disease control and available systemic options. Radiotherapy may provide symptom relief in selected patients with focal, bulky or symptomatic disease, whereas systemic therapy is selected according to primary tumor biology and prior treatment, and intrathecal therapy is generally considered for patients with tumor cells in the CSF and/or linear leptomeningeal disease when CSF flow is unobstructed (28,29). In the present case, irinotecan plus S-1 and WBRT were initiated, but rapid clinical deterioration, myelosuppression and intolerance prevented completion of the planned radiotherapy and precluded meaningful assessment of treatment efficacy.

Prognosis after meningeal dissemination from esophageal or gastroesophageal carcinoma is poor (3,35). The present patient succumbed ~2 months after radiological identification of probable meningeal metastasis, which is within the short survival range reported in previous series of meningeal metastasis from esophageal or gastroesophageal carcinoma (3,35). Early recognition is nevertheless clinically important, as it can avoid preventable diagnostic delay, permit timely symptom-directed treatment and multidisciplinary assessment, and align treatment intensity with neurological status and goals of care.

Three clinical lessons emerge. First, a recent SARS-CoV-2 infection should not deter urgent structural evaluation of a new, progressive or pupil-involving cranial neuropathy in a patient with cancer. Second, the pattern of ocular motor deficits can rapidly localize disease to the cavernous sinus and guide focused imaging interpretation. Third, extracranial disease control does not exclude CNS-predominant progression, particularly after a previous brain metastasis.

The principal limitation of the present study is the absence of CSF cytology, biochemical analysis and a biopsy of the cavernous sinus-adjacent or other meningeal lesions. Consequently, metastatic involvement was not pathologically confirmed, and the precise distribution between pachymeningeal and leptomeningeal compartments could not be established. The diagnosis was therefore based on the oncological history, neuroanatomical localization, short-interval serial MRI progression and enhancement pattern. Microscopic leptomeningeal disease and non-metastatic mimics cannot be excluded with absolute certainty.

In conclusion, for clinicians involved in oncological care, this case offers three practice-relevant messages: Do not attribute a new focal cranial neuropathy to recent SARS-CoV-2 infection without structural evaluation, use the pattern of ocular motor deficits to localize the lesion and do not assume that extracranial disease control excludes CNS progression. Early recognition enables timely multidisciplinary assessment and symptom-directed care.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HDZ and BH were responsible for the clinical management of the patient, retrieval and review of the patient's

medical records, treatment history, imaging examinations and follow-up information, preparation of the figures and drafting of the manuscript. JJP assisted with retrieval, verification and organization of the patient's clinical, treatment and follow-up data and contributed to manuscript drafting and revision. TY and FYK were responsible for diagnostic evaluation, imaging interpretation, and providing treatment recommendations, and they critically revised the manuscript. LZ was responsible for conceptualization, supervision, critical revision for important intellectual content, and final approval of the manuscript. HDZ and BH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the General Hospital of Western Theater Command of the Chinese People's Liberation Army and was granted an exemption from obtaining informed consent to participate due to its retrospective nature.

Patient consent for publication

After the patient's death, written informed consent was obtained from the patient's son, allowing the publication of anonymized clinical details and images.

Competing interests

The authors declare that they have no competing interests.

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