Choroidal metastasis as the first sign of small cell lung cancer: A case report

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Abstract. Metastases in the choroid originating from small cell lung cancer (SCLC) remain rare. The diagnosis of ocular metastases and primary lung tumors in individuals with SCLC can be challenging and time-consuming, particularly when their first symptoms present as ocular. The treatment of patients with ocular metastases of lung cancer is another clinical challenge in terms of primary tumor control and metastasis suppression. The current study presents the case of a 62-year-old man admitted to The Second Hospital of Jilin University (Jilin, China) for blurred vision. Based on subsequent clinical and pathological features of the patient, choroidal metastasis was suspected. Upon examination, the patient was diagnosed with serous retinal detachment, pleural effusion, choroidal metastases and SCLC of the right lung. Patients with the aforementioned condition receive chemotherapy and radiotherapy. First-line chemotherapy regimens consisted of etoposide and nedaplatin, while second-line regimens consisted of liposomal paclitaxel combined with lobaplatin. The condition of the patient was controlled during the first treatment period, which led to a temporary improvement in quality of life. However, the disease rapidly progressed, and the patient declined further treatment and ultimately succumbed to his illness. Visual symptoms may be the first indication of malignant tumors; therefore, ocular symptoms should be vigilantly monitored in patients diagnosed with malignant tumors. Furthermore, palliative care, psychological support and socioeconomic assistance are key to the quality of life of patients. Adoption of a patient-centered approach to provide comfort can also optimize treatment outcomes and improve the quality of life of patients.

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Abbreviations: SCLC, small cell lung cancer; OS, overall survival; RAI, right-anterior-inferior; RPI, right-posterior-inferior; CK, cytokeratin; CgA, chromogranin A; Syn, synaptophysin; CD, cluster of differentiation; TTF-1, thyroid transcription factor-1; LCA, leukocyte common antigen; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging

Key words: small cell lung cancer, choroidal metastasis, case report, chemotherapy resistance, ocular metastasis

Introduction

Lung cancer markedly impacts global health due to its high incidence and mortality with ~2.4 million new cases and 1.8 million deaths reported annually worldwide (1). Among various subtypes of lung cancer, small cell lung cancer (SCLC) is the most aggressive, characterized by rapid progression and early metastasis. Notably, 67% of patients with SCLC present with metastases at initial diagnosis, which commonly affects the brain, liver, adrenal glands, bone and contralateral lung (2).

Ocular metastases from lung cancer are rare, with the choroid being the predominant intraocular site. Metastasis to the eye predominantly involves the choroid (90%) and, less frequently, the iris (8%) and ciliary body (2%), as well as other intraocular structures (3). Choroidal metastases typically manifest with visual disturbances, including decreased visual acuity, blurred vision, photopsia, floaters, metamorphopsia and diplopia, although asymptomatic presentation may occur in certain cases (4).

This predilection for metastasis to the choroid is attributed to its vascular anatomy, which is supplied by multiple posterior ciliary arteries. The combination of sluggish blood flow, high vascular density and absent lymphatic drainage facilitates tumor cell deposition (5). Besides hemodynamic factors, organ-specific metastasis involves interactions between tumor cells and the host's microenvironment. Therefore, to enhance understanding of this rare presentation and optimize clinical pathways, this case report aims to describe the diagnostic and therapeutic challenges encountered in a patient with SCLC whose initial manifestation was blurred vision secondary to choroidal metastasis and retinal detachment.

Case report

A 62-year-old man presented to the ophthalmology clinic of The Second Hospital of Jilin University (Jilin, China) in December 2017 with painless visual impairment in the right eye. During the ophthalmological examination, the following findings were observed: A transparent cornea, a round pupil measuring 3 mm in diameter, a positive pupillary light reflex and a cloudy lens.

Digital ocular fundus imaging revealed a subretinal lesion temporal to the optic disc and notable retinal detachment in the lower region (Fig. 1). Ultrasound imaging demonstrated ciliary body leakage into the right eye, with a low-to-medium solid mass echo on the fundus bulb wall. This mass echo had an uneven internal echo and a clear boundary, with a membranous bulge noted on its surface. Color Doppler flow imaging exhibited abundant blood flow within the membranous mass, indicating intraocular tumor or metastasis (Fig. 2). Optical coherence tomography revealed a prominent macular protrusion (Fig. 3). Angiography demonstrated a prominent and compact mass in the right eye with an elevated momentum underneath and fluorescein and indocyanine green angiography indicated blood vessel leakage and scattered areas of intense fluorescence (Fig. 4). The definitive diagnosis of choroidal metastases remains challenging compared to choroidal melanoma or hemangioma due to overlapping clinical features, similar imaging characteristics and the low incidence of this condition (6-8). Therefore, dynamic MRI scans were performed with both plain and contrast-enhanced imaging of both eyes, which demonstrated a tumor in the right eyeball characterized by choroidal metastasis with concurrent retinal detachment (Fig. 5).

Following an initial diagnosis of choroidal metastasis, a systematic search for the primary tumor was conducted. Chest CT imaging revealed a heterogeneously enhancing mass (46x35 mm) in the right lower lung lobe, accompanied by suspected malignant pleural effusion and probable metastatic involvement of right hilar/mediastinal lymph nodes (Fig. 6). Histopathological examination of transbronchial biopsy specimens that had been formalin-fixed and paraffin-embedded (FFPE) (following standardized dewaxing, rehydration, routine hematoxylin and eosin staining, dehydration and mounting of paraffin sections) was performed using a light microscope (BX51; Olympus Corp.), and revealed sheets of atypical cells with hyperchromatic nuclei and scant cytoplasm, characteristic of poorly differentiated carcinoma. Cellular morphology indicated nuclear molding and crush artifacts, which strongly suggested small cell carcinoma (Fig. 7). Immunohistochemical staining was performed on FFPE tissue samples. Tissue sections (3 μm thick) mounted on adhesive glass slides were dewaxed in xylene (3x10 min) and rehydrated through graded ethanols (100%, 2x5 min; 95, 85 and 75%, each for 2 min). Permeabilization was not specifically applied. Endogenous peroxidase activity was blocked using peroxidase blocking reagent (ready-to-use; Fuzhou Maixin Biotechnology Development Co., Ltd.) for 30 min at room temperature, followed by non-specific blocking with blocking reagent (ready-to-use; Dako; Agilent Technologies, Inc.) for 30 min at room temperature. The following primary antibodies were applied: Anti-Cytokeratin AE1/AE3 [CK(AE1/AE3); monoclonal antibody; cat. no. A500-019A; Thermo Fisher Scientific, Inc.]; anti-chromogranin A (CgA; polyclonal antibody; cat. no. ab15160; Abcam); anti-synaptophysin (Syn) (monoclonal antibody; cat. no. ab32127; Abcam); anti-cluster of differentiation 56 (CD56/NCAM; monoclonal antibody; cat. no. 313602; BioLegend); anti-Ki-67 (monoclonal antibody; cat. no. M7240; Dako; Agilent Technologies); anti-thyroid transcription factor-1 (TTF-1) (monoclonal antibody; cat. no. MS-063-P; Cell Marque); anti-leukocyte common antigen (CD45) (monoclonal antibody; cat. no. 555482; BD Biosciences); anti-napsin A (monoclonal antibody; cat. no. CM007A; Biocare Medical); anti-p40 (ΔNp63; monoclonal antibody; cat. no. CM163A; Biocare Medical); and anti-CK5/6 (monoclonal antibody; cat. no. M7237; Dako; Agilent Technologies). Secondary detection used biotin-labeled goat anti-mouse/rabbit IgG polymer (UltraSensitive SP kit; ready-to-use; Fuzhou Maixin Biotechnology Development Co., Ltd.) for 30 min at room temperature, followed by streptavidin-HRP (UltraSensitive SP kit; ready-to-use; Fuzhou Maixin Biotechnology Development Co., Ltd.) for 30 min at room temperature. Stained slides were examined using a light microscope (BX51; Olympus Corp.) at x100 magnification. The staining revealed the following: CK(AE1/AE3) (+), CgA (+), Syn (+), CD56) (+), Ki-67 (90%), TTF-1 (+), CD45 (-), Napsin A (-), p40 (-) and CK5/6 (-). These findings confirmed the diagnosis of SCLC. Subsequent CT and whole-body bone scan corroborated the final diagnoses of serous retinal detachment, malignant pleural effusion, choroidal metastases and SCLC of the right lung.

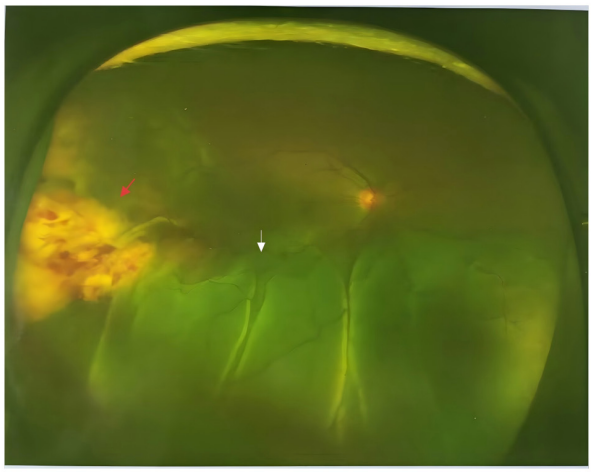

Figure 1. Fundus photograph of the right eye at initial consultation shows a subretinal lesion temporal to the optic disc (red arrow), with inferior retinal detachment (white arrow).

The patient was administered the etoposide and nedaplatin regimen (EP regimen) (etoposide 100 mg/m^2 + nedaplatin 80 mg/m^2, once every 3 weeks). The chemotherapy dosage and treatment intervals were adjusted based on the tumor burden and physical condition of the patient. After four cycles of EP chemotherapy, follow-up lung CT in May 2018 demonstrated a notable therapeutic response: The primary tumor (pre-treatment size, 46x35 mm) in the right lower lobe showed regression to a 15x15 mm nodular shadow, with concomitant reduction in mediastinal lymphadenopathy (Fig. 6). This radiographic improvement was consistent with partial remission according to the Response Evaluation Criteria In Solid Tumors (9). Notably, serous retinal detachment and choroidal metastases remained stable on concurrent ophthalmologic evaluation.

The patient underwent six cycles of chemotherapy with the EP regimen, achieving a partial response, which demonstrated the efficacy of the treatment. However, after 5 cycles of chemotherapy, the ocular symptoms of the patient were exacerbated. Shortly thereafter, the patient experienced complete vision loss in the right eye, along with redness, swelling and increased blood flow in the surrounding area. The retina exhibited a

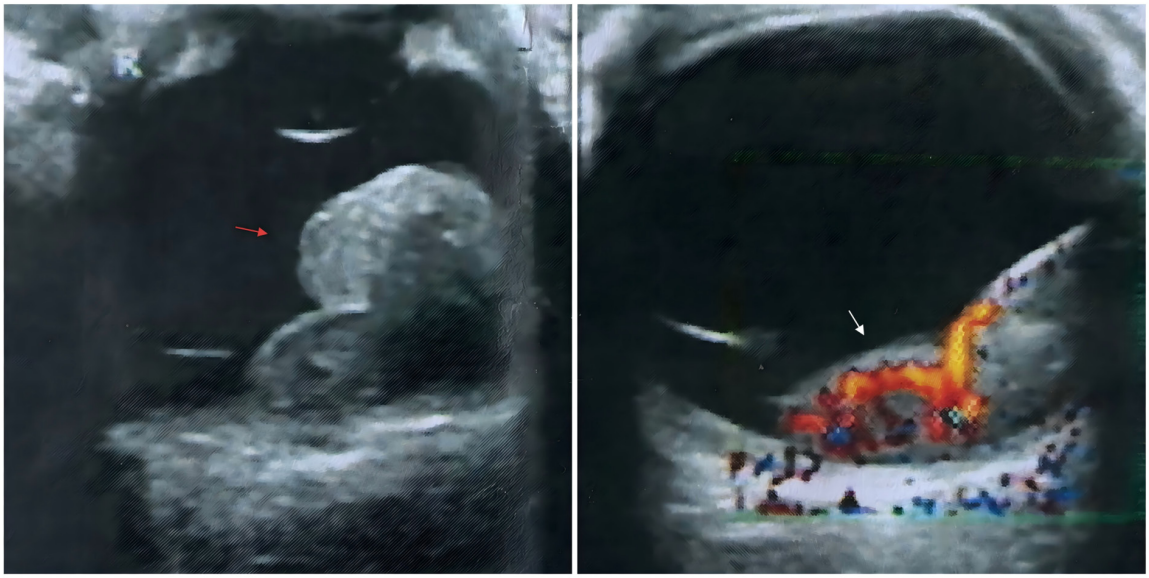

Figure 2. Ocular ultrasound at initial consultation shows ciliary body leakage and a low-to-medium echogenic solid mass on the fundus wall (red arrow), with irregular internal echoes and well-defined margins. A membranous bulge with abundant internal blood flow is observed (white arrow).

large blue-gray swelling with no light reflection. The patient then underwent localized radiation therapy to relieve ocular discomfort.

In September 2018, within 3 months following the completion of chemotherapy, the patient presented again to the Second Hospital of Jilin University (Jilin, China) with a headache on the right side. The patient exhibited electrolyte abnormalities and elevated tumor markers (neuron-specific enolase elevation, CA125 elevation, hyponatremia, hypokalemia). A chest CT revealed an enlarged area of dense opacities in the right lung and an MRI of the head indicated an abnormal signal in the right cerebellar hemisphere (Fig. 8), which suggested metastasis and local recurrence of the extensive stage SCLC in the patient.

Given that patients with this condition typically receive an EP regimen with a response duration of <3 months, primary resistance to the initial regimen was suspected (10). In SCLC treatment, lobaplatin, as a third-generation platinum agent, exhibits lower cross-resistance compared with first- and second-generation platinum drugs (11). The patient currently has an Eastern Cooperative Oncology Group (ECOG) performance status (12) of 0 and a numerical rating scale pain score (13) of 3. In addition to controlling disease progression to extend survival, contemporary treatment strategies prioritize pain management and enhancement of quality of life. Therefore, the lobaplatin-liposomal paclitaxel combination was chosen for palliative treatment (liposomal paclitaxel 135 mg/m^2 + lobaplatin 50 mg, once every 3 weeks). After completing the lobaplatin-liposomal paclitaxel combination treatment regimen, the patient discontinued further therapy and succumbed to his illness in December 2018.

Discussion

Choroidal metastases are the most common site of intraocular metastases, which accounted for 80-90% of cases in previous studies (14-16). Of these, breast cancer is the most common cause, accounting for 37-47% of all reported cases. Furthermore, lung cancer is another important cause, being the origin of 21-44% of all reported cases of choroidal metastases (16-18). Due to its increased aggressiveness and potential for hematogenous dispersion, lung carcinoma has a higher propensity for ocular metastasis compared with other solid tumors (19-21).

Adenocarcinoma is the most common histological type of lung cancer in patients with choroidal metastasis of lung cancer, followed by squamous cell carcinoma and SCLC (22,23). Among the subtypes of lung carcinoma, SCLC has a markedly higher incidence of choroidal metastasis compared with non-SCLC (NSCLC), likely due to its higher malignant potential and early hematogenous dissemination (24-26). SCLC choroidal metastasis is often bilateral and multifocal, characterized by rapid growth and sensitivity to chemotherapy; however, it has a higher likelihood of drug resistance and shorter survival (median, 3-6 months) (20,26). Unilateral involvement is uncommon in ocular metastases from lung cancer, accounting for only 12% of cases (20,25,27). Although precise incidence data for SCLC choroidal metastasis are limited, its clinical significance as a rare initial symptom is substantial and warrants high vigilance.

The mechanism underlying vision loss due to choroidal metastasis is multifaceted and involves various factors, such as direct compression of tumors, retinal detachment, vascular changes and inflammatory responses (28).

Choroidal metastases are frequently underdiagnosed due to their asymptomatic presentation or nonspecific ocular symptoms (e.g., visual field defects, photopsia), which lead to potential underestimation of their true incidence (29,30). After an actual diagnosis of lung cancer, some cases have been identified using systematic screening techniques (such as fundoscopy, ultrasonography or optical coherence tomography). In patients with SCLC, notable systemic metastases or concurrent brain metastases often overwhelm ocular evaluations, which delays diagnosis (31,32). However, when patients

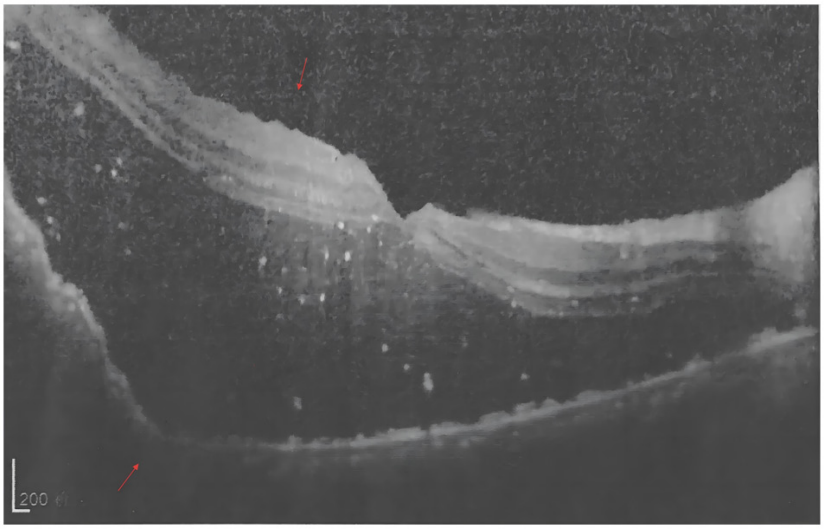

Figure 3. Optical coherence tomography at initial consultation shows elevation of the retina with associated inferior retinal detachment (red arrow) (scale bar, 200 μm).

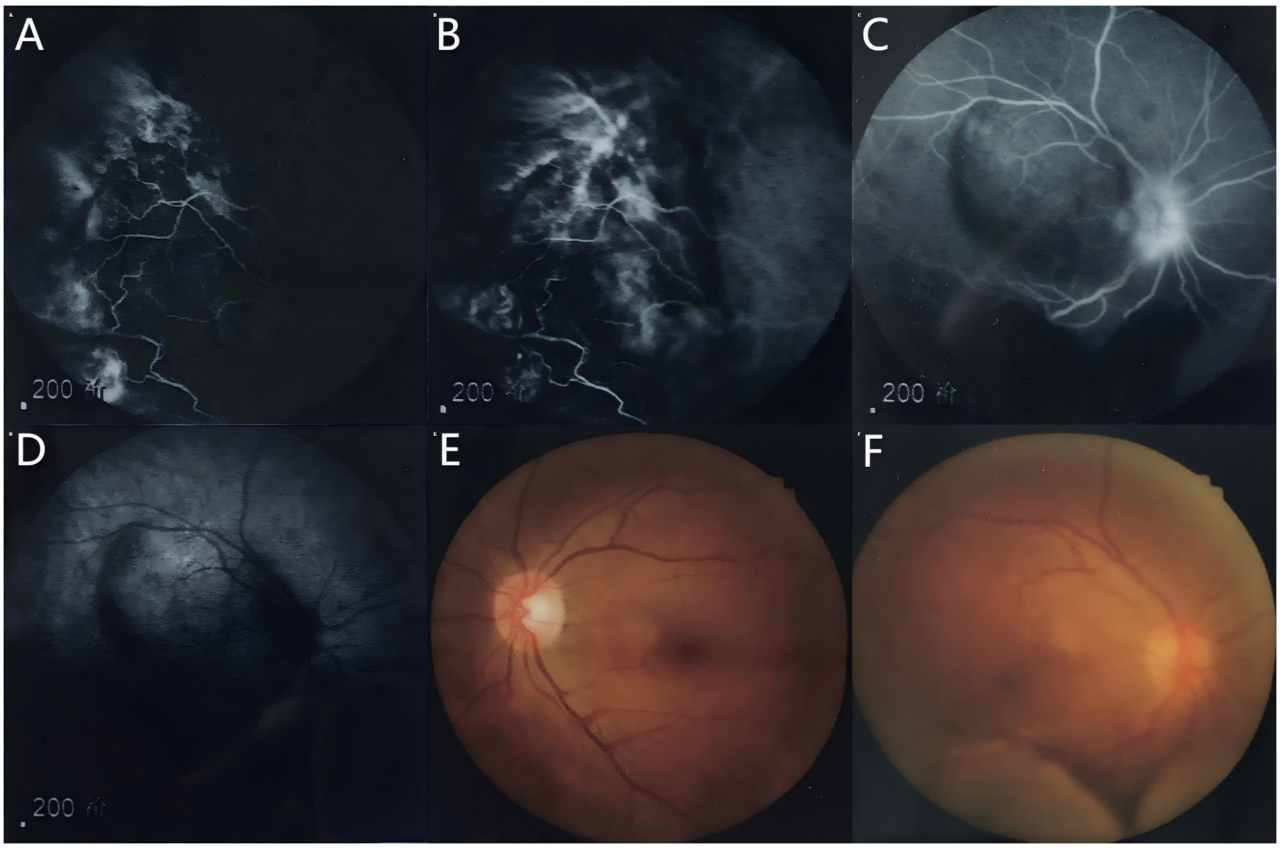

Figure 4. Multimodal fundus images at initial presentation showing a vascularized intraocular lesion (magnification, x200). (A) Early-phase FA shows intense hyperfluorescence and active leakage in the right eye. (B) Early ICGA reveals a dense choroidal vascular network in the right eye. (C) Late-phase FA demonstrates persistent dye pooling and staining in the right eye. (D) Late-phase ICGA shows localized choroidal hyperfluorescence in the right eye. (E) Color fundus photo of the left eye is unremarkable. (F) Color fundus photo of the right eye shows a yellowish elevated lesion.

with undiagnosed cancer present with visual impairment, the integration of imaging techniques (e.g., MRI/CT) with histopathological confirmation via fine-needle aspiration biopsy achieves diagnostic accuracy exceeding 90% (33). Several recent reviews and systematic studies recommend baseline ophthalmic evaluations for patients with SCLC to enhance early detection rates and optimize prognostic outcomes (34,35).

Choroidal metastasis from SCLC is characterized by acute visual impairment, with a markedly faster symptom progression compared with other metastatic intraocular tumors, such as breast or renal carcinoma. The typical signs of choroidal

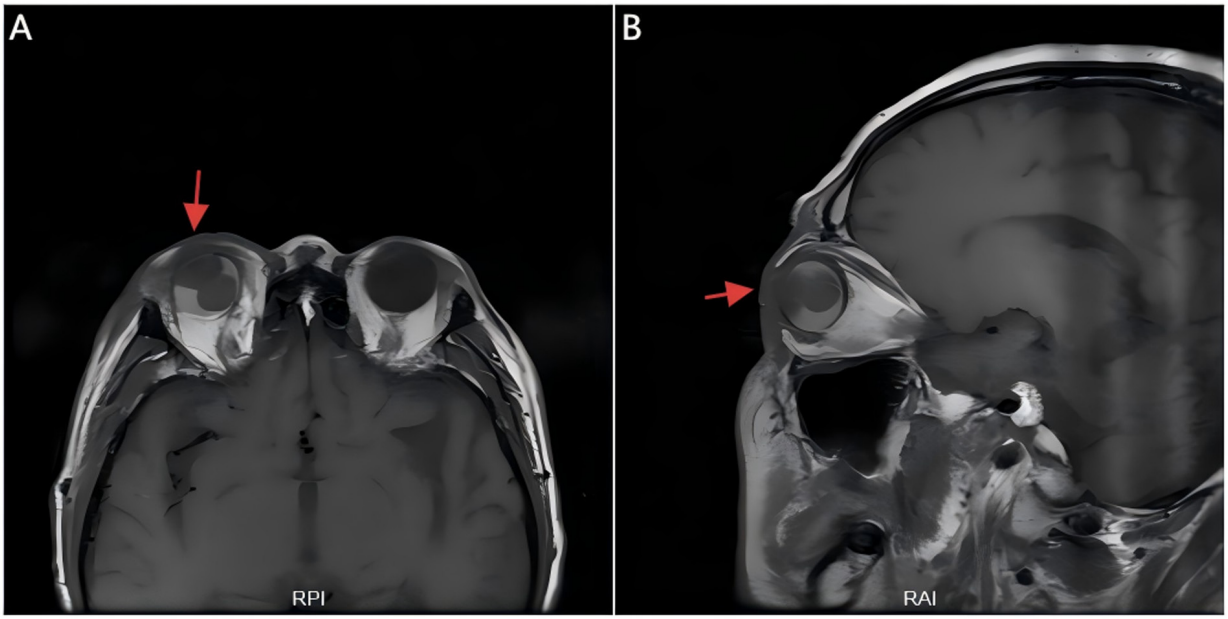

Figure 5. Orbital MRI showing choroidal metastasis in the right eye. (A) Axial view reveals an intraocular mass with associated retinal detachment (red arrow). (B) Sagittal view confirms choroidal thickening and elevation of the retina (red arrow). RAI, right-anterior-inferior; RPI, right-posterior-inferior.

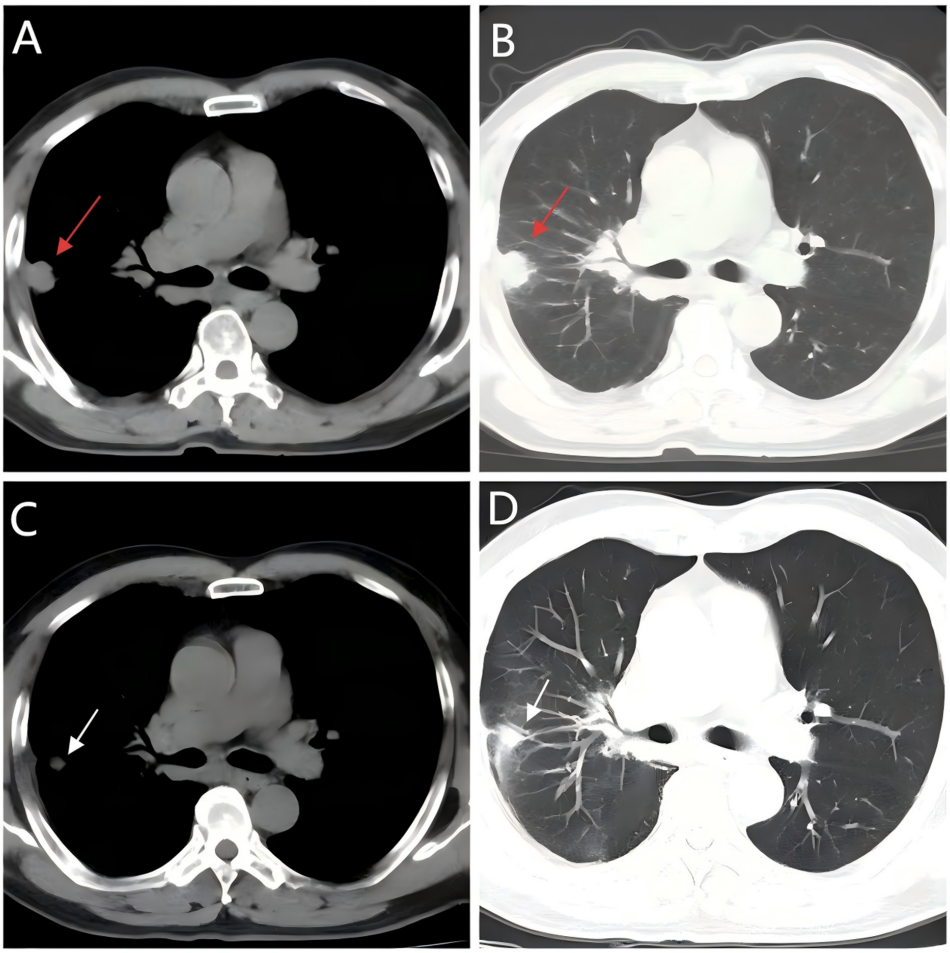

Figure 6. Axial chest CT scans before and after treatment. (A) Pre-treatment CT (mediastinal window) reveals a heterogeneously enhancing mass (46x35 mm) in the right lower lung lobe with suspected malignant pleural effusion and right hilar/mediastinal lymphadenopathy (red arrow). (B) Pre-treatment CT (lung window) reveals decreased aeration in the right lower lobe due to compression by the mass, along with visible pleural effusion. (C) Post-treatment CT (mediastinal window) reveals reduction in the mass size, resolution of pleural effusion, and improved lung clarity in the right lower lobe (white arrow). (D) Post-treatment (lung window) reveals improved lung clarity in the right lower lobe and re-expansion of the compressed lung tissue, with no evident pleural effusion.

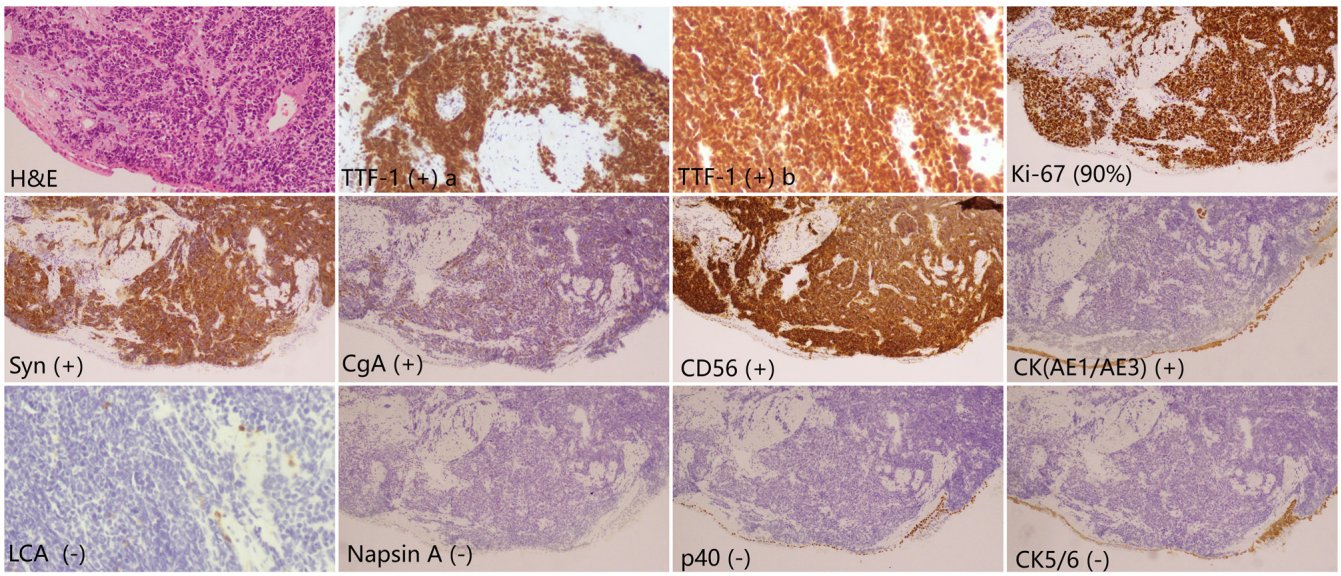

Figure 7. Histopathological and immunohistochemical analysis of the pulmonary lesion obtained via transbronchial biopsy. Cellular morphology shows nuclear molding and crush artifacts, consistent with small cell carcinoma. Immunohistochemistry reveals positivity for CK(AE1/AE3), CgA, Syn, CD56, Ki-67 (90%) and TTF-1, and negativity for LCA/CD45, Napsin A, p40 and CK5/6 (magnification, x100). CK, cytokeratin; CgA, chromogranin A; Syn, synaptophysin; CD, cluster of differentiation; TTF-1, thyroid transcription factor-1; LCA, leukocyte common antigen.

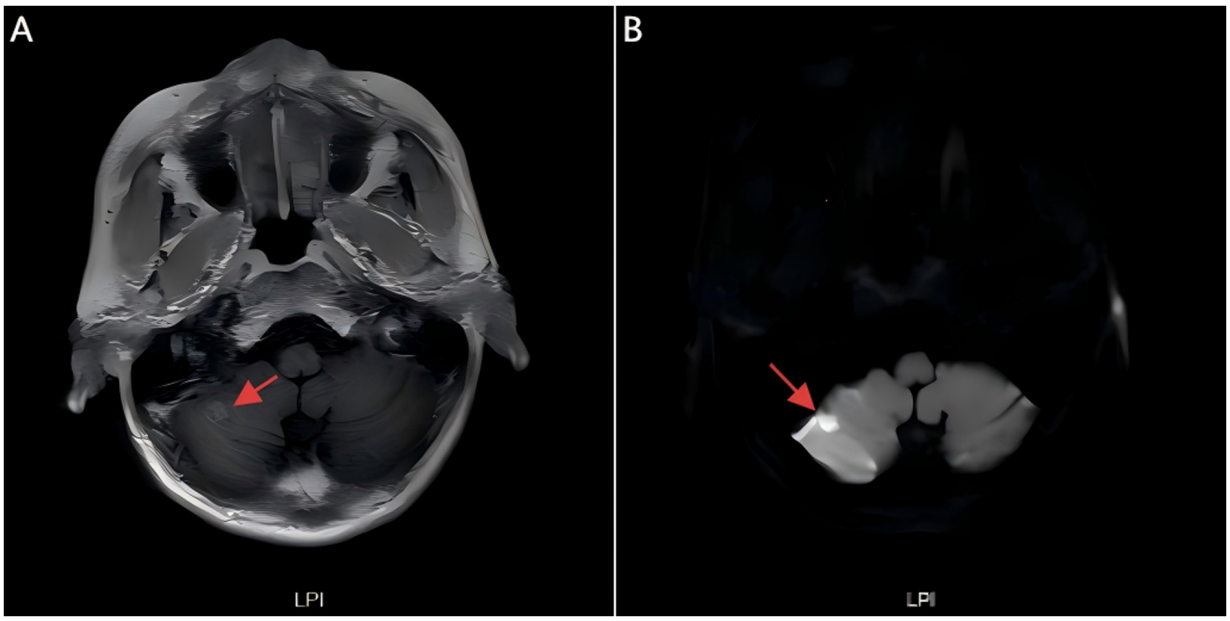

Figure 8. Brain MRI showing abnormal signal in the right cerebellar hemisphere. (A) Axial T1-weighted image (red arrow). (B) Diffusion-weighted imaging reveals a hyperintense lesion (red arrow).

metastasis include flat, yellowish-white lesions in the posterior pole of the fundus, which often grow infiltratively and are frequently associated with serous retinal detachment, important clinical clues for identification (36). Compared with other primary tumors, such as breast cancer, SCLC-related choroidal metastases are more likely to present as multifocal and have a notably higher rate of bilateral involvement compared with NSCLC, which indicates a more aggressive biological behavior (37).

Given these clinical manifestations, multimodal imaging techniques are key to a definitive diagnosis. It is essential to integrate radiological, metabolic and molecular biological evidence to clarify the nature of the lesion and trace the primary site. Ultrasound biomicroscopy can precisely measure lesion thickness and has a significantly higher detection rate for micro-metastases compared with conventional B-mode ultrasound (38). Optical coherence tomography angiography technology can be used to analyze the microvascular patterns of choroidal metastases and identify specific microvascular structural features of choroidal metastases, which provides important evidence for their diagnosis (39). In high-risk patients, whole-body positron

emission tomography (PET)-CT and single-photon emission CT bone scans can be useful diagnostic tools for the identification of metastases.

The systemic treatment of SCLC with choroidal metastasis should consider primary tumor control and metastasis suppression. According to the 2025 National Comprehensive Cancer Network guidelines (40), the combination of etoposide and platinum (EP regimen) as first-line therapy achieved an objective response rate of 68-75%, with a median progression-free survival of 5.2 months, and it remains the standard regimen for extensive-stage SCLC.

Recent years have witnessed breakthroughs in systemic therapeutic strategies for SCLC. Novel evidence from multiple phase III clinical trials and meta-analyses (41-45) has established programmed cell death protein 1/programmed cell death-ligand 1 inhibitors combined with platinum-etoposide regimens as the first-line standard of care for extensive-stage SCLC in both National Comprehensive Cancer Network and Chinese Society of Clinical Oncology guidelines, with their survival benefits, particularly the notable improvement in median overall survival (OS), which achieved broad clinical validation.

Emerging evidence further highlights the therapeutic importance of integrating multi-targeted antiangiogenic agents with immunochemotherapy for SCLC (46-48). A recent randomized phase 3 trial demonstrated that this combinatorial approach achieved a median OS of 19.3 months compared with 11.9 months in the control group, which corresponded to a 38% reduction in mortality risk (hazard ratio=0.61; P=0.0002) (49).

Radiotherapy constitutes a cornerstone of SCLC management, which serves as a key component in both primary tumor control and metastatic disease targeting. Conventional external beam radiotherapy is currently the standard radiation technique for the treatment of choroidal metastases, which provides tumor control (response or stability) in ~90% of all cases (50). Stereotactic radiosurgery has been demonstrated to effectively reduce tumor volume and attenuate signs of fibrosis during follow-up (51). Intravitreal injection of bevacizumab can alleviate macular edema and improve visual acuity (52). The clinical efficacy of ophthalmic treatments appears promising, particularly for patients with a short life expectancy. Minimally invasive procedures can enhance quality of life and minimize ocular toxicity.

The advent of precision medicine is ushering in novel dimensions for individualized SCLC management through the strategic convergence of molecular subtyping-guided multi-target interventions and immune microenvironment modulation. Future translational research must prioritize the optimization of therapeutic efficacy via multidisciplinary collaboration underpinned by multi-omics biomarker profiling, which thereby addresses the long-standing challenges posed by SCLC.

Of note, the present study had certain limitations. PET-CT was not performed during initial staging or post-chemotherapy evaluation due to financial constraints of the patient. Although conventional imaging modalities (including chest CT, head CT, abdominal CT, whole-body bone scintigraphy and brain MRI) provided sufficient evidence for the diagnosis of extensive-stage SCLC, the absence of PET-CT may limit the precise assessment of metabolic activity in metastatic lesions.

In conclusion, the importance of a multidisciplinary team co-led by ophthalmologists and oncologists, as well as the integration of radiology, pathology and radiotherapy knowledge for diagnosis and treatment, is highlighted in the present case. Additionally, throughout the treatment and follow-up phases of patients with malignant tumors, relevant vision tests and fundus monitoring methods should be included in the follow-up plans to identify ocular metastases as early as possible. Finally, patients need not only palliative care but also economical and psychological support, which can optimize treatment continuity and lower the risk of treatment cessation. This case underscores the need for comprehensive diagnostic and management strategies to improve early detection, treatment continuity and quality of life in patients at risk for ocular metastases.

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Availability of data and materials

The data generated in the present case report are included in the figures of this article.

Authors' contributions

KW conceptualized the present case report, wrote the original draft and reviewed and edited the manuscript. FL systematically collected and verified clinical records, imaging, pathology, and follow-up data and devised the methodology. CN performed the formal analysis. CH acquired funding, provided project administration, resources and supervised the present case report. YZ prepared the study documents, wrote the original draft, conducted literature review, contributed to differential diagnosis and drafted clinical implications. CH directed diagnostic strategy, validated clinico-pathological correlations, interpreted oncology data, critically revised manuscript. KW and CH validated the data and visualized the data in the present case report. KW and CH confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present case report adheres to ethical guidelines outlined in the Declaration of Helsinki. Ethical approval for the present case report was provided by the Ethics Committee of the Second Hospital of Jilin University (approval no. 2024-348) on August 26, 2024.

Patient consent for publication

Informed consent was obtained from the patient and his family members for the publication of anonymized clinical details, images and data in May 2018.

Competing interests

The authors declare that they have no competing interests.

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