Right eye metastasis of small-cell lung carcinoma: A case report

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Abstract. The incidence of eye metastasis from primary malignant tumors is low. Predominantly, these primary malignant tumors consist of breast and lung carcinoma. Ocular metastatic carcinoma is often clinically overlooked. In clinical practice, it is rare for small-cell lung carcinoma (SCLC) to metastasize to the right eye. Early detection and treatment via the monitoring of clinical symptoms and auxiliary examinations of the eye are of great significance in preserving the patient's vision and improving their quality of life. Such treatments include radiotherapy or enucleation of the eyeball. A 54-year-old male patient with SCLC experienced a decline in vision and blurred vision during his systemic treatment using combined enverolumab and etoposide and cisplatin. Upon examination, including fundus photography, ocular B-scan and magnetic resonance imaging, a right eye metastasis was suspected. Within a short period of time, the patient experienced significant pain and blindness in the right eye, which required surgical removal of the right eyeball. Postoperative pathology confirmed metastasis. After six cycles of treatment, the primary lesion in the lung reduced in size. By reporting this case of SCLC metastasis to the right eye, we aim to provide a reference for the clinical diagnosis and treatment of ocular metastatic carcinoma.

Introduction

Lung carcinoma is one of the most common malignant tumors in China, with an incidence rate that ranks second in the country; moreover, it has a mortality rate that ranks first globally (1). Lung carcinoma is classified into non-small-cell lung carcinoma (NSCLC) and small-cell lung carcinoma (SCLC), of which SCLC accounts for ~15% of lung carcinomas (2). SCLC is characterized by a high proliferation rate, a tendency for early metastasis and a poor prognosis (3). Most patients with SCLC have already developed distal metastasis at the time of diagnosis. Intraocular tumors can threaten the patient's vision and even life. Moreover, symptoms of ocular metastatic carcinoma can be the same or similar to symptoms of the primary tumor (4). Therefore, ocular metastatic carcinoma is easily overlooked, making accurate diagnosis and treatment more crucial. Case reports regarding eye metastasis in SCLC indicate that right-sided eye metastasis is rare (5). The present study reported a case of SCLC with right-sided eye metastasis. It gives a comprehensive report of the patient's treatment process, in order to provide a reference for the clinical diagnosis and treatment of ocular metastatic carcinoma.

Case presentation

A 54-year-old male patient presented with right flank pain and limited mobility of the right lower limb, accompanied by numbness, which began in April 2023. In June 2023, the patient was treated at Lu'an Hospital, which is affiliated with Anhui University of Chinese medicine (Anhui, China). A lumbar magnetic resonance imaging (MRI) scan indicated a high possibility of bone metastasis (Fig. 1E and F). A further contrast-enhanced chest computed tomography (CT) revealed a malignant lesion at the hilum of the left lung with pleural metastases (Fig. 1A and B). Cranial MRI suggested a possible metastatic lesion in the right eye (Fig. 2A and D). The patient underwent a pulmonary tissue biopsy and subsequent immunohistochemical staining.

The lung tissue was immersed in 4% neutral formalin at 37˚C for 24 h. It was then dehydrated with different concentrations of ethanol and finally embedded in paraffin. A 4 μm tissue section adhering to the glass slide was baked in a 60˚C oven for 1.5 h. Subsequently, an immunohistochemical experiment was conducted using the Roche BenchMark XT fully automated immunohistochemical instrument (Roche Diagnostics). Detailed operational procedures were as follows: Heat dewaxing was performed using EZ Prep (dehydrating solution, 1:10, lot number: K14102; Roche Diagnostics). Then, CC1 (alkaline repair solution, pH 8.0-8.5, lot number: 77307801; Roche Diagnostics) was applied at 100˚C for a given period of time (depending on the type of antibody), with an increase in heating time of 8 min and a cooling time of 7 min. Blocking was performed using a UV Inhibitor (hydrogen peroxide, lot number: K13635-K13800; Roche Diagnostics) for 4 min. A primary antibody was added and the mixture incubated for a specified period of time. The antibodies with an antigen retrieval time of 36 min included: CD56 (rabbit

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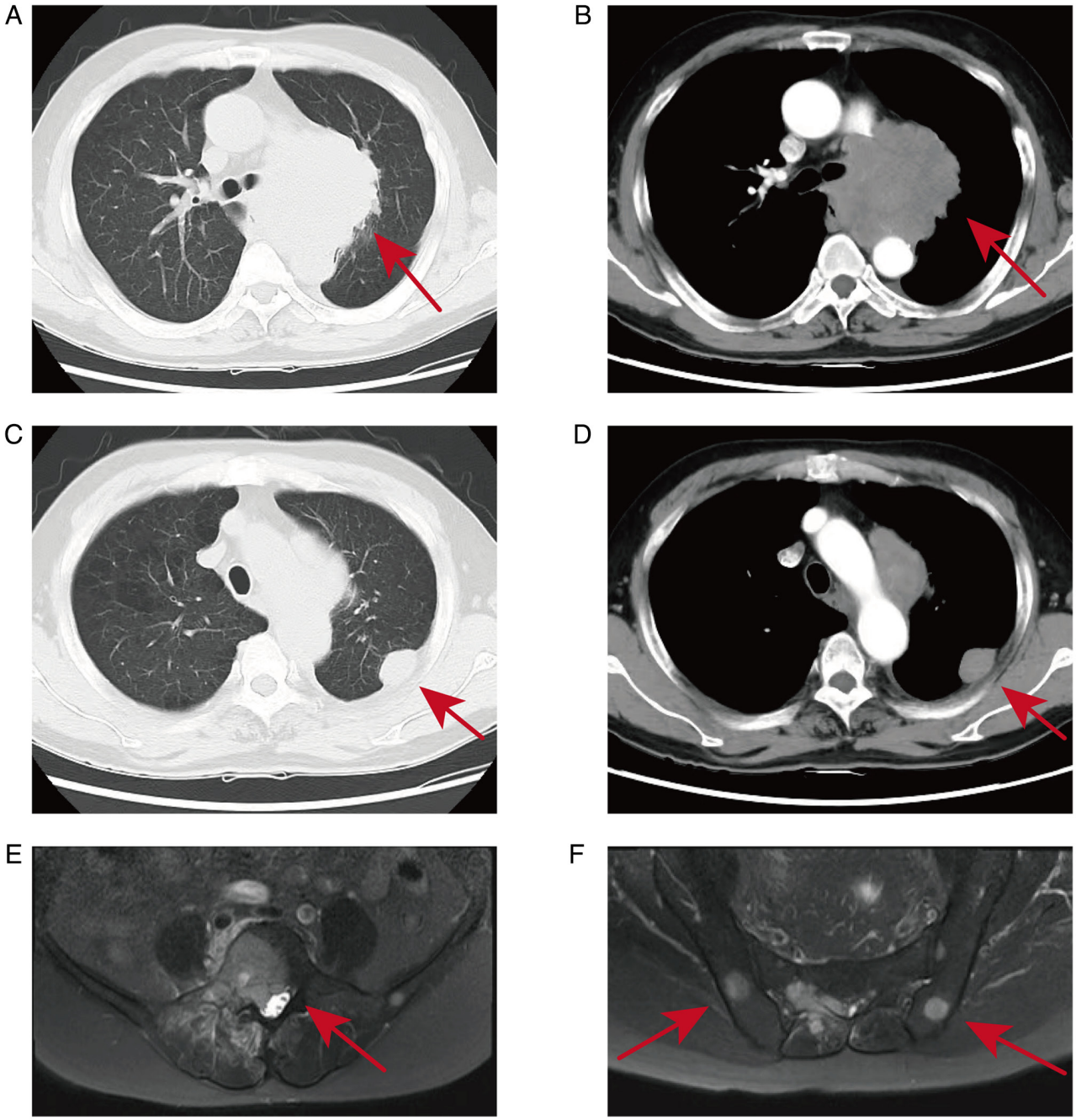

Figure 1. Contrast-enhanced chest computed tomography and lumbar magnetic resonance imaging. (A and B) The lesion at the left hilum of the lung has merged with the lymph nodes in zones 3P, 6 and 7, with a maximum diameter of ~83 mm (Red arrow). The trachea at the left hilum of the lung has been compressed and narrowed. (C and D) A soft tissue-like lesion is visible near the pleura in the dorsal segment of the left middle lung. It has a well-defined boundary and dimensions of ~24.9x18.5 mm (Red arrow). (E and F) Abnormal signals were detected in the vertebral body and bilateral ilium (Red arrow).

monoclonal, cat. no. IR040; incubation time: 36 min), CK5/6 (mouse monoclonal, lot no. IM060; incubation time: 36 min), NapsinA (mouse monoclonal, cat. number: IM198; incubation time: 40 min), Ki-67 (rabbit monoclonal, lot number: IR098; incubation time: 40 min). The antibodies with an antigen retrieval time of 64 min included: P40 (rabbit monoclonal, lot number: IR345; incubation time: 36 min), TTF-1 (rabbit monoclonal, lot no. IR301; incubation time: 36 min), CgA (mouse monoclonal, lot number: IM053; incubation time: 40 min), LCA (mouse monoclonal, lot number: IM038; incubation time: 40 min) (all antibodies were stock solutions from Abcam; temperature was 37˚C). The UV HRP-Multimer (the second antibody, comprising HRP-labeled goat anti-mouse IgG, goat anti-mouse IgM and goat anti-rabbit antibodies, ~55 μg/ml, lot number: K13635-K13799; Roche Diagnostics) was added to the mixture and incubate for 8 min. UV DAB (3,3'-diaminobenzidine reagent; lot number: K13635-K13802; Roche Diagnostics) and UV H_2O_2 (phosphate buffer solution containing 0.04% hydrogen peroxide, lot number: K13635-K13803; Roche Diagnostics) were added and incubate for 8 min. UV Copper (an enhancer containing 5 g/l copper sulfate, lot number: K13635-K13805; Roche Diagnostics) was added and incubate for 4 min. Hematoxylin II (lot number: K14384; Roche Diagnostics) was added and incubated for 12 min. bluing

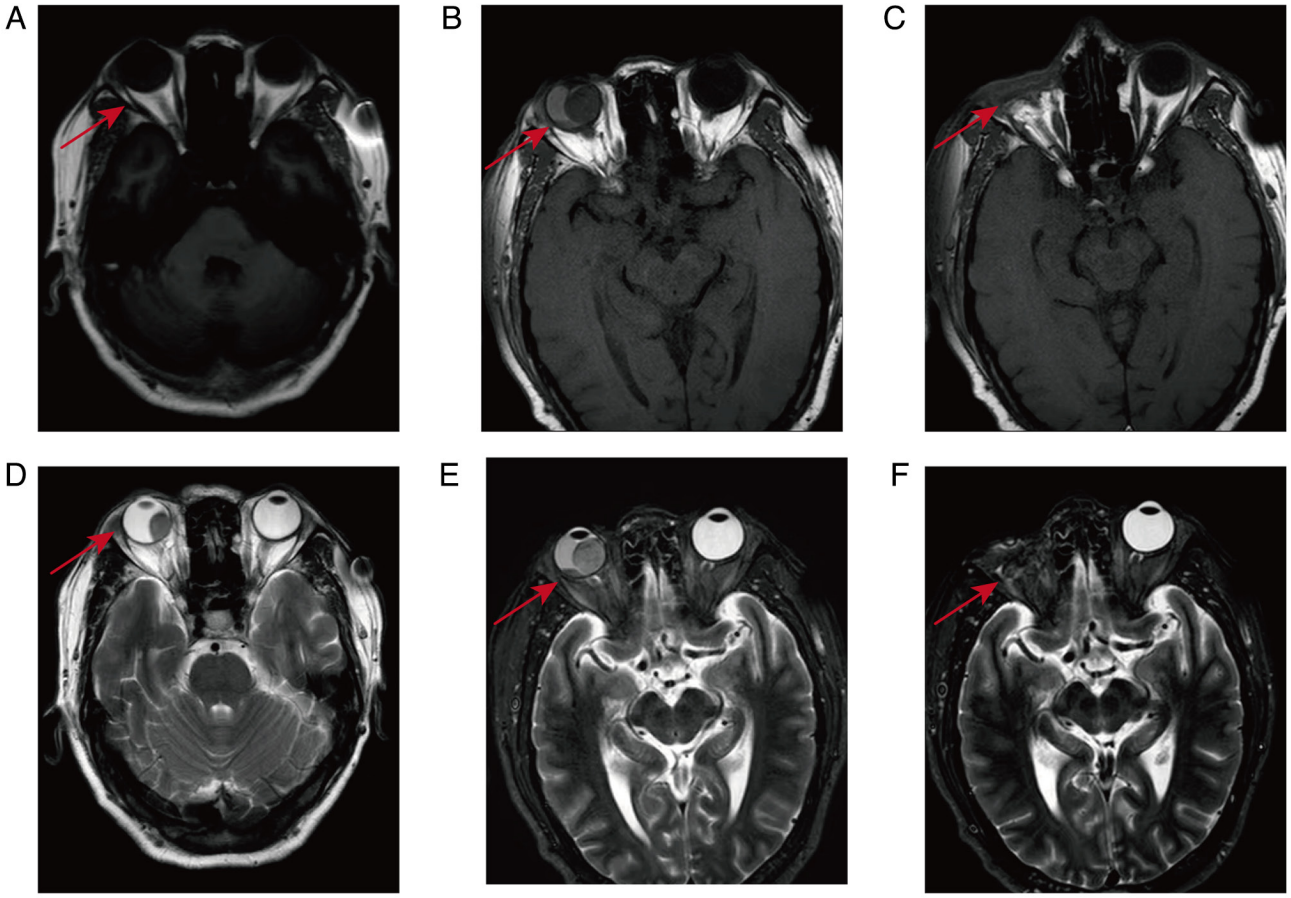

Figure 2. Cranial MRI and contrast-enhanced MRI of the orbits. (A and D) A lesion with slightly low T1 and equal T2 signal intensity is observed within the right eyeball. It has a clear boundary and dimensions of ~16x11 mm. After contrast administration, the lesion shows significant enhancement (Red arrow). (B and E) A lesion with slightly low T1 and equal T2 signal intensity is observed within the right eyeball, with a well-defined boundary and dimensions of ~14x5 mm. Post-contrast enhancement revealed a mildly uneven intensification of the lesion. Additionally, a cystic lesion with slightly high T1 and slightly high T2 signal intensity is visible on the lateral margin. Post-contrast enhancement shows high signal intensity, with dimensions of ~15x7 mm (Red arrow). (C and F) Absence of the right eyeball (Red arrow). MRI, magnetic resonance imaging.

reagent (lot number: K12265; Roche Diagnostics) was added and incubated for 4 min. Upon completion, The tissue sections on the slides were dehydrated, mounted in a neutral resin and then imaged using an optical microscope.

Based on the results of lung histopathology (Fig. 3) and immunohistochemistry (IHC; Fig. 4A-D) and after ruling out other neuroendocrine tumors, the patient was diagnosed with SCLC of the left lung, stage T4N1M1c, IVB. The patient did not have a family history of hereditary diseases. The patient is divorced and has one daughter. The patient has been smoking for >30 years.

Starting in June 2023, the patient was treated with envero-lumab and etoposide and cisplatin every three weeks as a course of treatment: Enverolumab 400 mg subcutaneously on day 1; Etoposide 120 mg intravenously on days 1-3; and Cisplatin 30 mg intravenously on days 1-3. In July 2023, after one course of treatment, the patient experienced decreased and blurred vision in both eyes. The ophthalmological consultation indicated that the intraocular pressure of both eyes was as follows: Right/left: 16/18 mmHg. Right fundus photography (Fig. 5A) and right eye ultrasound (Fig. 5B-C) showed a space-occupying lesion in the vitreous chamber and retinal detachment in the right eye. The treatment plan primarily focused on systemic therapy. In August 2023, after two courses of treatment, the patient experienced

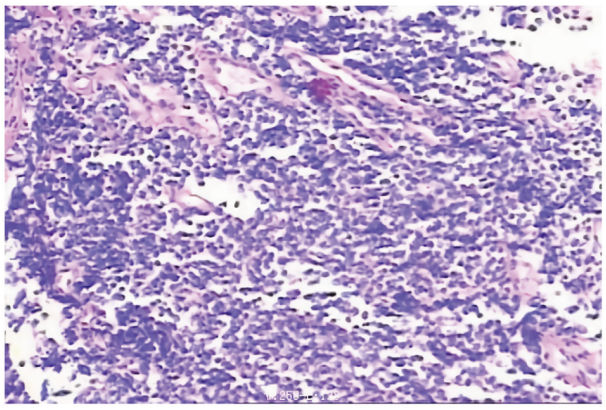

Figure 3. Quick paraffin-embedded lung tissue histopathology (Hematoxylin and eosin staining, magnification, x100). (Left upper lung) Malignant tumour, consistent with small-cell carcinoma based on immunohistochemical markers.

pain in the right eye. The ophthalmologic consultation indicated an intraocular pressure of 32 mmHg in the right eye. The contrast-enhanced MRI of the orbits showed abnormal enhancement signals and a detached state of the retinal membrane on the right eyeball (Fig. 2B and E). At 4 days later, there was significant

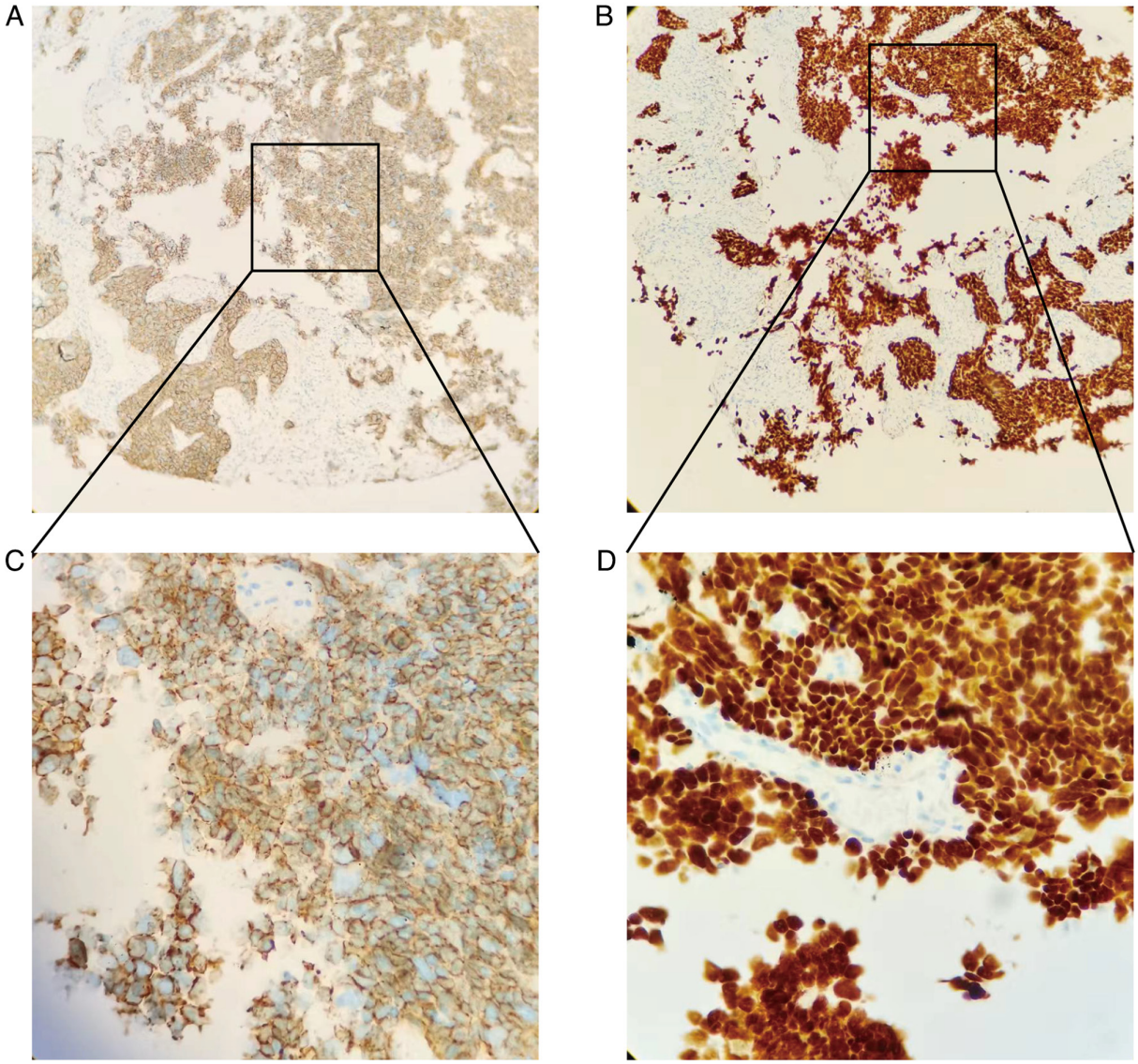

Figure 4. Immunohistochemistry. (A) CD56(+). (B) TTF-1(+). Magnification, x100). (C) CD56(+) (magnification, x400). (D) TTF-1(+). Magnification, x400).

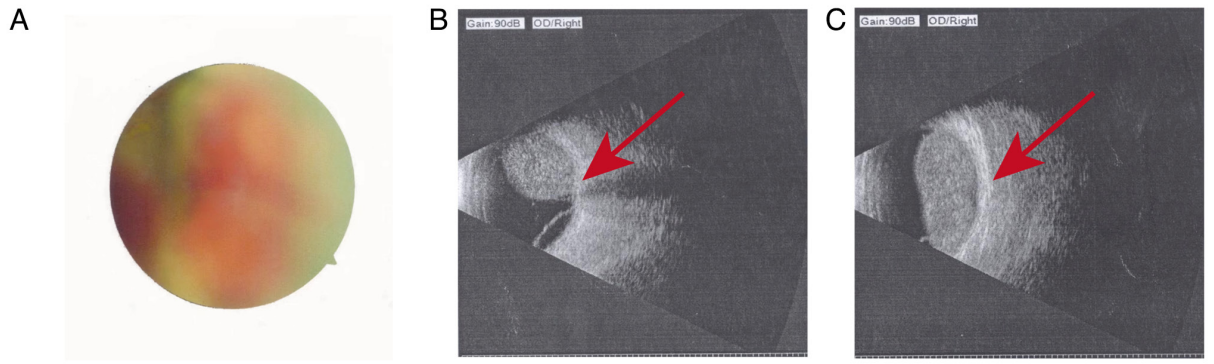

Figure 5. Right eye fundus photography and right eye ultrasound. (A) The right eye shows a significant elevation of the retina, with a pale colour and a well-defined margin of the optic disc, while the other structures are not clearly visible. (B and C) In the vitreous cavity, there are visible clumps of high reflectivity connected to the spherical wall, with stripes of high reflectivity below (Red arrow).

conjunctival congestion in the right eye (Fig. 6A and B). Within a week, the patient reported experiencing total blindness in the right eye and the oral oxycodone dose was rapidly increased to 40 mg every 12 h (q12h). Following consultations with a multiple disciplinary team (MDT), it was decided not to opt for ocular radiation treatment due to the absence of visual acuity in the right eye. Even if radiation therapy proved to be effective, visual acuity could not be restored. Later in August 2023, the patient

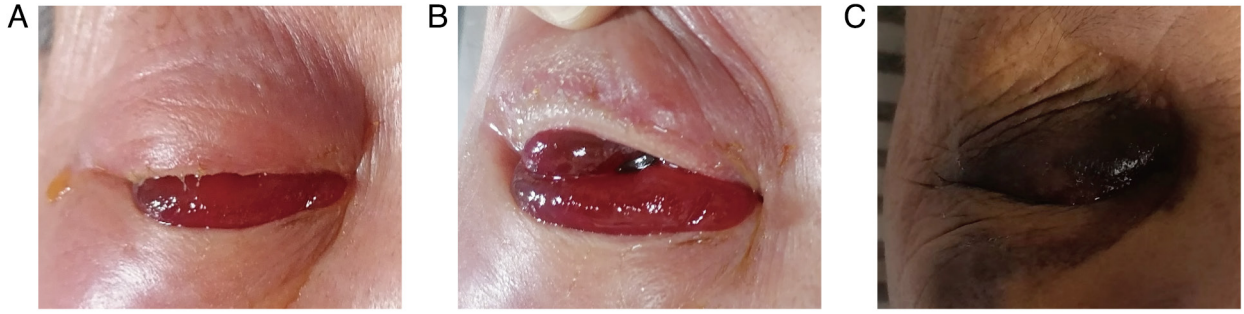

Figure 6. Right-sided view. (A and B) Ocular condition after two treatment sessions. (C) Post-enucleation surgery.

underwent enucleation of the right eyeball. This was performed at the 901 Hospital of the People's Liberation Army of China, which is located in Hefei, Anhui (China). The patient provided the hospital's postoperative pathology and immunohistochemical results. Postoperative pathology revealed a small-cell malignant tumor in the right eyeball (Pathology Report Number: 2306821). When the patient's IHC results were examined in combination with the medical history, there was a tendency for pulmonary small-cell metastasis to the right eyeball. The tumor measured 2x2x1.3 cm and invaded the retina and choroid, but not the sclera. IHC (23-506) results were as follows: TTF-1(-), P40(-), Syn(+), NapsinA(-), CD56(+) and CgA(-). The Ki-67 hotspot area covered ~70%. The patient continued to be treated at Lu'an Hospital (Anhui, China). The postoperative recovery of the eye was good (Fig. 6C). After four courses of treatment, a contrast-enhanced MRI of the orbits was performed in September 2023. This showed the absence of the right eyeball, with no metastatic lesions in the left eye (Fig. 2C and F). In October 2023, by the sixth course of treatment, the contrast-enhanced chest CT showed that the hilar and pleural metastatic lesions had reduced in size compared to June (Fig. 7A-D). During the treatment period, the levels of carbohydrate antigen 125 (CA-125), neuron-specific enolase (NSE) and progastrin-releasing peptide (ProGRP) decreased (Fig. 8). In addition, the demonstrated vertebral metastases were treated with radiotherapy (30 Gy/10 fractions). Currently, the condition of the patient is stable, with ongoing oral administration of anlotinib (12 mg qd). In addition, follow-up visits are continuing.

Discussion

SCLC is a high-grade neuroendocrine carcinoma (6). It is an aggressive smoking-related malignancy characterized by rapid growth and early metastatic spread (7). Depending on the extent of tissue involvement, SCLC is generally divided into limited period and extensive stages (8). The extensive stage accounts for ~70% of SCLC cases (9), with the most common sites of metastasis being the brain, liver, or bone (10). There are also reports of ocular metastasis from SCLC (11).

Intraocular tumors are classified into primary and metastatic tumors. Metastatic tumors in the eye can originate from various tissues and organs throughout the body. The most common primary tumor sites that lead to intraocular metastasis are the breasts (40-47%) and lungs (21-29%) (12). Additionally, primary tumors in other locations can also metastasize to the eye, such as the kidney (13), stomach (14) and pancreas (15).

The eyes lack a lymphatic system, with most eye metastatic tumors arising from hematogenous spread (16). Metastatic tumors in the eye mainly occur in the uveal tissue due to its abundant blood supply and multiple vascular connections, with the choroid being the most frequent location (17). Intraocular metastatic tumors are relatively rare (18). The ophthalmic artery branches at a right angle to the internal carotid artery. This anatomical feature increases the likelihood of tumor emboli in the bloodstream getting lodged within the intracranial cavity due to the rapid blood flow. Consequently, these emboli are less likely to enter the eye through the ophthalmic artery. The incidence of intraocular metastases to the left eye may be slightly higher, based on anatomical characteristics (19). That is, the bloodstream of the right eye must bypass the innominate artery to travel upward, whereas the left common carotid artery can directly ascend into the left eye.

The most common ocular symptoms of intraocular metastasis are blurred vision and loss of vision (20). These often occur due to invasion of the macular area or the area around the optic disc, leading to subretinal exudation which causes retinal detachment. Other symptoms include eye pain, floating objects in the vision, visual field defects, abnormal eye position, proptosis, increased orbital pressure, diplopia and restricted eye movement.

The ocular manifestations of metastatic tumors may serve as the initial symptoms of the primary tumor (21-23). Misdiagnosis or missed diagnosis of eye metastases may lead to rapid deterioration of the condition. If detected late, it may invade the contralateral optic nerve along the orbital floor, leading to bilateral vision loss and potentially blindness (24-26). Within the clinical literature, there are cases of ocular metastatic carcinomas misdiagnosed as secondary glaucoma, leading to vision loss and the need for enucleation of the eyeball (27). Therefore, for patients suspected of having metastatic carcinoma in the eye, early diagnosis is crucial. This can be achieved through a comprehensive evaluation of the patient's signs and symptoms, as well as necessary auxiliary examinations, to formulate an appropriate treatment plan.

Clinical manifestations serve as the basis for the early diagnosis of eye metastases. If a patient shows signs of suspected malignant tumors in the eyes, an immediate examination should be conducted to identify potential orbital metastases. Diagnostic confirmation can be achieved through a comprehensive array of modalities, including: funduscopy, ocular ultrasound, optical coherence tomography (OCT),

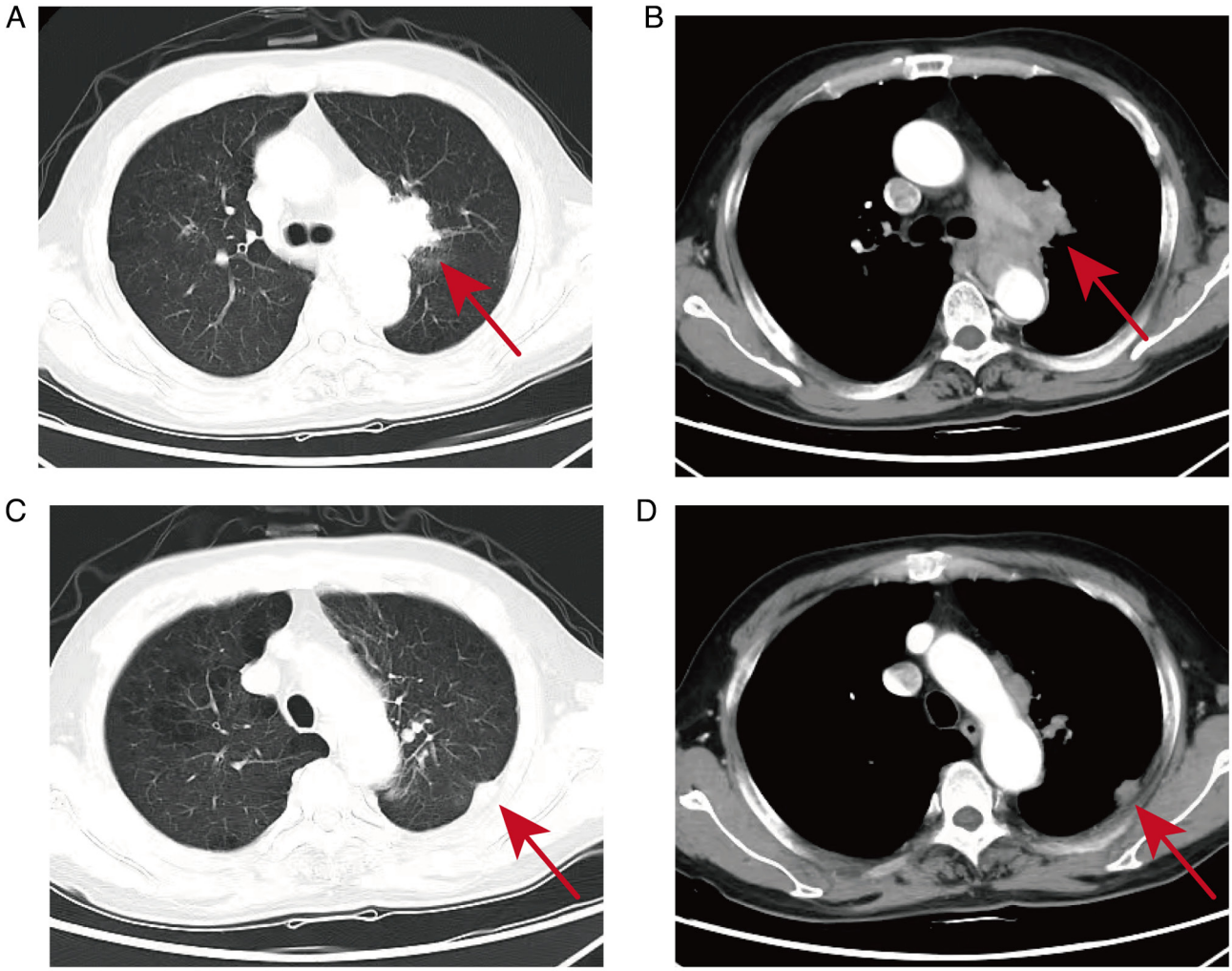

Figure 7. Contrast-enhanced chest CT. (A and B) Multiple ring-shaped enhancing nodules are observed at the left lung hilum, appearing as fused masses, with the largest one measuring ~24 mm in diameter (Red arrow). (C and D) A soft-tissue lesion near the pleura was identified in the dorsal segment of the left mid-lung. It has a clear margin and dimensions of ~15.3x11.9 mm (Red arrow).

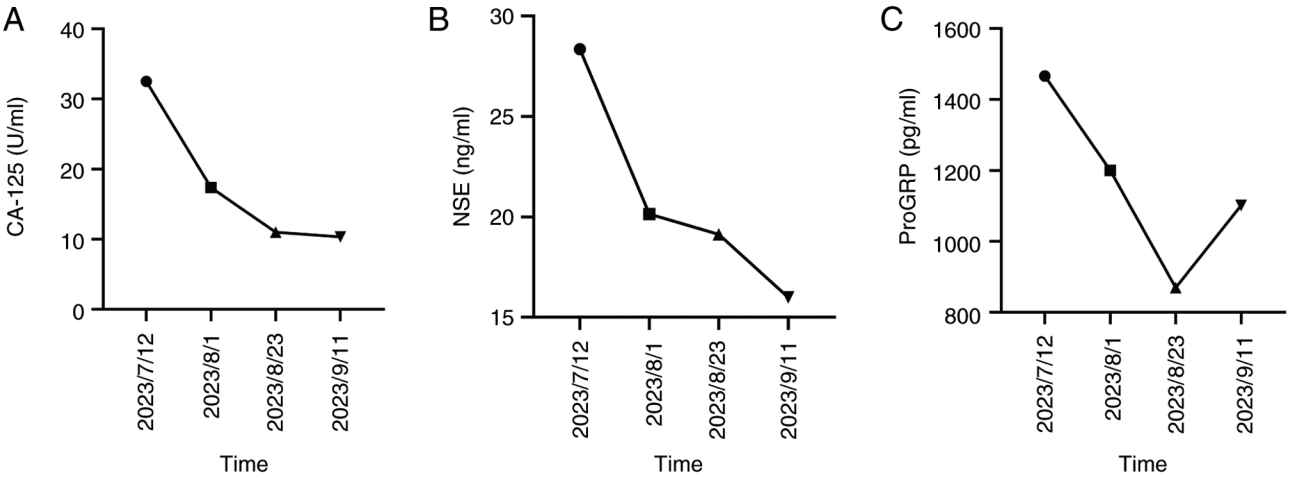

Figure 8. Blood test indicators. (A) CA-125 is a carbohydrate antigen, with a normal range of 0.00-35.00 U/ml. (B) NSE has a normal range of 0.00-16.30 ng/ml. (C) ProGRP has a normal range of 8.3-74.4 pg/ml. CA-125, cancer antigen 125; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide.

fundus fluorescence angiography (FFA), indocyanine green angiography, CT, MRI and, when necessary, histopathological examination via fine-needle aspiration biopsy (FNAB) (28).

The treatment for intraocular metastatic tumors primarily involves systemic and localized therapies (29). However, systemic treatment often leads to secondary resistance. For

eye metastases, local treatment is recommended either concurrently or following systemic therapy (30). Radiation therapy is the primary localized treatment for eye metastases (31). Ocular radiation therapy can eradicate localized tumors, control pain and improve vision. Specifically, studies have indicated that in a group of 15 patients (19 eyes) who underwent reflexotherapy, 11 out of 13 (84.6%) showed improvement in vision and 14 out of 15 (93.3%) experienced partial or complete remission (CR) of their ocular tumors (32). When the ocular metastatic carcinoma causes severe pain or discomfort that cannot be alleviated by medication or other conservative treatments and the eyeball loses its normal function, enucleation of the eyeball may be performed.

The use of enverolumab as a treatment was based on the protocol provided by the Cancer Hospital, which is affiliated with the Fudan University in Shanghai, China. After patient consultation, the patient's family requested the use of this protocol. According to the Chinese Society of Clinical Oncology guidelines, enverolumab is not recommended as a first-line treatment for extensive small cell lung carcinoma (ES-SCLC). However, a review of relevant literature revealed clinical studies on the use of a combination of enverolumab with carboplatin/cisplatin and etoposide as a first-line treatment for ES-SCLC (33). Therefore, the hospital's recommendation was followed and this protocol was accordingly implemented.

In the present case, the patient experienced a sudden loss of vision and intense pain in the right eye within a short period of time. Upon examination using funduscopy, ophthalmic ultrasound, OCT and eye MRI, a metastatic lesion was suspected. After MDT consultations, surgical extraction was chosen. Postoperatively, the patient's pain and quality of life improved markedly. Systemic treatment using immunotherapy combined with chemotherapy resulted in a decrease in lung lesions. However, eyeball extraction is a destructive procedure that should be performed cautiously when multiple lines of evidence are established. If possible, hospitals should conduct multidisciplinary discussions. If the patient's eye pain is not severe, local radiation therapy should be the first choice. Early diagnosis and treatment of the ocular metastatic carcinoma can help control tumor spread, preserve vision and improve the patient's quality of life. When clinical symptoms suggest a suspected malignant tumor in the eye, a comprehensive cancer investigation should be conducted using funduscopy, ophthalmic ultrasound, OCT, FFA, CT, MRI and FNAB. Timely and appropriate treatment should be provided to preserve the patient's vision as much as possible and manage the growth of intraocular tumors.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

QS developed a clear treatment plan for patients with SCLC. During the treatment WD collected detailed cases. MW collated the patients' cases and pictures. PZ collected relevant literature, wrote, translated and refined the manuscript. Finally, all individuals checked the data and completed this article. PZ and WD confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient's written consent has been obtained.

Competing interests

The authors declare that they have no competing interests.

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