• Review Article •

Rapid progress of an iris metastasis from esophageal cancer: a case report and review of literature

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Abstract

● This case report details a rare instance of rapid iris metastasis from esophageal cancer in a 59-year-old man. A literature review was conducted to explore recent advances in detecting, diagnosing, and treating intraocular metastatic malignancies. Positron emission tomography-computed tomography played a crucial role in identifying primary sites and systemic metastases. Local treatment combined with systemic therapy effectively reduced tumor size, preserved useful vision, and improved the patient's survival rate. A comparison was made of the characteristics of iris metastases from esophageal cancer and lung cancer, including age, gender, tumor characteristics, and treatment. The challenges associated with diagnosis and treatment are discussed, highlighting the implications for clinical practice.

● **KEYWORDS:** iris metastasis; esophageal cancer; positron emission tomography-computed tomography; review
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INTRODUCTION

Intraocular malignant tumors, as a vision-threatening disease, damage patients' vision and endanger their survival. Malignant tumors in the eye may originate primarily from ocular tissues or may be secondary to cancer metastases elsewhere in the body. Metastatic intraocular tumors usually reach intraocular structures *via* hematogenous spread. The rate of intraocular metastasis has been reported to be as high as 12%[1]. In terms of incidence, intraocular metastases of malignant systemic tumors are the most common intraocular tumors, with ten times more frequent than primary intraocular tumors[2]. Intraocular malignancies usually originate from primary breast cancer (37%–47% of cases) and lungs (20%–27% of cases). The most frequent primary sites are the lungs in males and breasts in females, respectively[3-4]. Intraocular metastases commonly occur in the uveal tract. Reportedly, 9% of metastases occur in the iris, and only 2% occur in the ciliary body[5]. Therefore, as a disease accounting for only 8% of cases of uveal metastasis, iris metastases from systemic cancer are uncommon[6-7].

Most cases of uveal metastasis have a known primary focus; however, ocular manifestations may be the first indication of disseminated malignant disease in approximately one-third of the cases[8]. Due to the poor prognosis of patients, accurate differential diagnosis, identification of the primary tumor, and earliest possible application of treatment are necessary[9]. Herein, we reported an infrequent case of esophageal cancer metastasis to the iris. The patient's clinical, imaging, and histological features were briefly described, and he underwent positron emission tomography-computed tomography (PET/CT) scanning. At the same time, we performed a literature review on iris metastasis and summarized its clinical manifestations from esophageal cancer and lung carcinoma to highlight the characteristic features of iris metastasis and the importance of prompt diagnosis and management of ocular tumors.

Case Presentation A 59-year-old man developed ocular pain in his right eye for a month with no history of significant weight loss or other medical conditions. Ophthalmic examination showed best-corrected visual acuity of 20/30 in the right eye (OD) and 20/30 in the left eye (OS). The intraocular pressure (IOP) was 21 mm Hg OD and 15 mmHg OS. At presentation, anterior segment examination of the right eye showed a pinkish, vascularized neoplasm located on the temporal iris, expanding the 6-clock to 9-clock anterior chamber angle. The pupil was compressed into a crescent

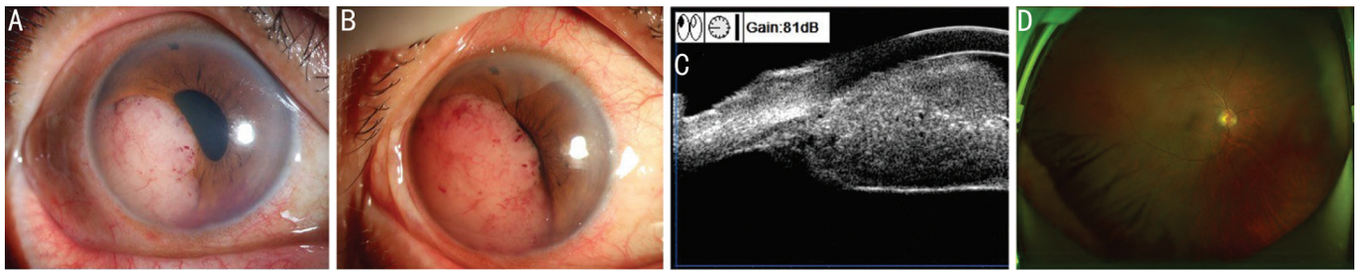

Figure 1 Eye examination of the patient A: Iris metastasis at 2022-08-22; B: Iris metastasis at 2022-08-30, the volume of the mass increased significantly compared to that of eight days earlier; C: Ultrasound biomicroscopy showing that the mass has blocked part of the anterior chamber angle and is attached to the corneal endothelium; D: Fundus examination revealing a clear optic disc boundary and no obvious swollen lesion in the choroid.

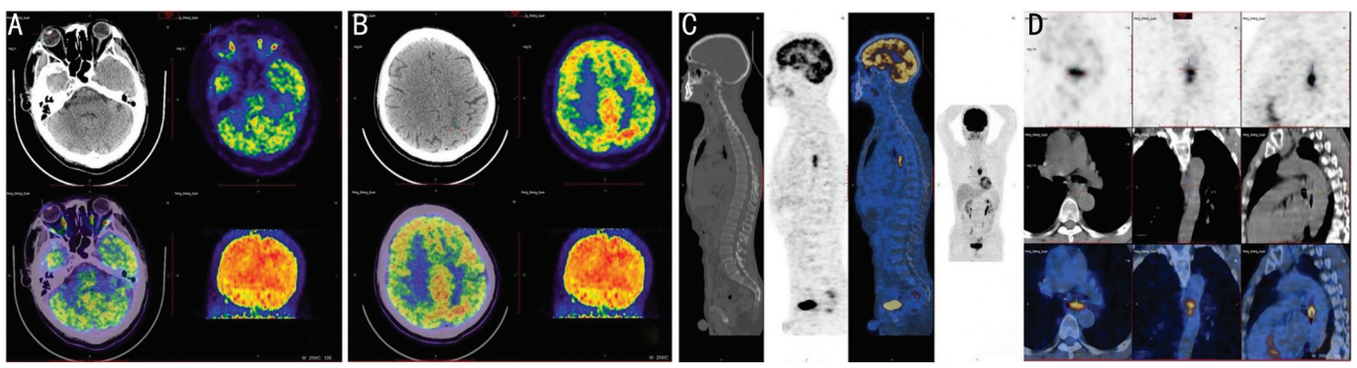

Figure 2 Imaging manifestations of the patient CT shows a high-density shadow in the right anterior segment (A). PET/CT revealing the high uptake of FDG in the anterior chamber space of the right eye (A), the middle esophagus (C, D) and left parietal lobe of the brain (B). CT: Computed tomography; PET/CT: Positron emission tomography-computed tomography; FDG: Fluorodeoxyglucose.

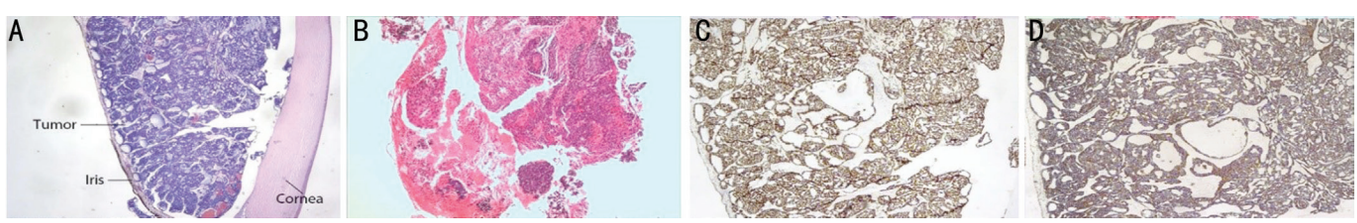

Figure 3 Histopathological findings of the patient Histopathologic examination showing squamous cell carcinoma in the eyeball (A) and esophagus (B). Immunohistochemical staining showing P40, P63 (C), and CK5/6 positivity (D).

shape by the lesion (Figure 1A). The tumor was significantly larger than it was 8d earlier (Figure 1B). Ultrasound biomicroscopy showed that the mass had blocked a part of the anterior chamber angle and was attached to the corneal endothelium (Figure 1C). Fundus examination revealed a clear optic disc boundary and no obvious swollen lesions in the choroid (Figure 1D). The left eye was normal. Computed tomography (CT) showed a high-density shadow in the right anterior segment (Figure 2A). PET/CT revealed high uptake of fluorodeoxyglucose (FDG) in the anterior chamber space of the right eye (Figure 2A), the middle esophagus (Figure 2C, 2D), and the left parietal lobe of the brain (Figure 2B). After systematic evaluation by the oncology department, enucleation was performed to confirm the source of the tumor. Histopathological examination revealed squamous cell carcinoma (Figure 3A). Immunohistochemistry was performed to differentiate between primary and metastatic iris mass lesions. Then, iris lesions were considered metastatic, with CK5/6 (Figure 3D) positivity and P63 (Figure 3C) and P40 positivity. The patient underwent esophagoscopy half a month later, and histopathological examination revealed esophageal squamous cell carcinoma (Figure 3B). Microscopically, the primary lesion from the esophageal biopsy and the metastatic iris lesion showed the same cell formation. The final diagnosis was esophageal cancer with multiple metastases. During follow up, the patient underwent radiotherapy for whole brain and esophageal neoplasia at a local hospital. However, esophageal cancer and brain metastases showed poor response to treatment, and the patient passed away one year after the initial ophthalmologic assessment due to systemic complications.

Ethical Approval This study was approved by the Ethics Committee of Wuhan Union Hospital (2021-0016) and complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient.

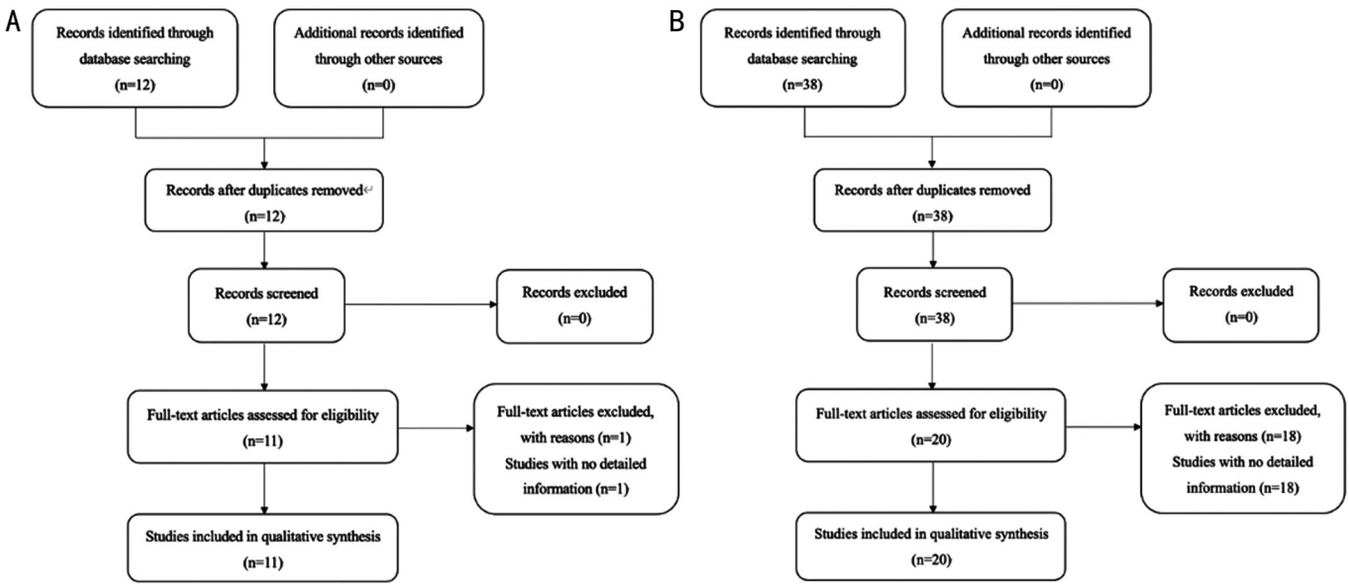

Figure 4 PRISMA flow diagram of study selection process A: Flow diagram of study selection process of esophagus cancer; B: Flow diagram of study selection process of lung cancer.

Literature Search Strategy The search strategy included the following terms: (iris metastasis) AND ("esophageal cancer" or "esophageal carcinoma") in PubMed published in English from 1987 to February 2022 and in CNKI published in Chinese. There were 10 studies from PubMed and 2 studies from CNKI. The literature was screened according to the following inclusion and exclusion criteria. Articles on cases diagnosed with iris metastasis from esophageal carcinoma with detailed data were included, and one study without full text was excluded. A total of 11 studies with 13 cases were retrieved. Meanwhile, we compared various parameters found in the literature with those of patients with iris metastases of lung cancer. In this paper, using "iris metastasis" and "lung" as keywords, literature on lung cancer with ocular metastasis was retrieved from PubMed. A total of 38 related studies were retrieved. Eighteen articles with missing clinical information were excluded after intensive reading. Finally, 20 case reports with a total of 20 patients were included in this study (Figure 4). We collected detailed information on the patients' characteristics, including their age and sex, and the characteristics of the iris metastasis, such as the affected side, eye symptoms, visual acuity, and IOP. The properties of the clump were also analyzed in detail. In addition, pathology, treatment, and prognosis are described in detail.

Summary of the Cases of Iris Metastasis of Esophageal Cancer What was unique about this case was that the patient's undiagnosed esophageal cancer initially presented as a symptomatic intraocular mass. There were only 13 cases that have reported the metastasis of esophageal carcinoma to the iris[10-20]. Table 1 summarizes important literature describing cases of iris metastasis from esophageal cancer. The patients were aged 53 to 77y, with a mean age of 61y, and were mainly men in this study. Iris metastasis can lead to various symptoms, including vision loss, eye pain, eye distension, and foreign body sensation. In this case, the patient presented with ocular pain. We observed that the tumor cells compressed the iris and blocked the anterior chamber angle, causing blockage of aqueous humor drainage. Iris metastases are characterized by turbidity of the aqueous humor, snowflake-like deposits, and nodular masses. However, the underlying mechanisms of the different iris appearances remain unknown. We hypothesized that the different shapes of iris metastases might be due to different primary tumor subtypes, stages, and patient visit times. Pathology of the iris metastasis revealed atypical cells, squamous cell carcinoma, mucoepidermoid carcinoma, and mucous-secreting adenocarcinoma. Four of these patients had no history of primary cancer, whereas the other eight patients had previous cancers, including esophageal squamous cell carcinoma and adenocarcinoma. Four patients were treated with radiotherapy alone, two received chemotherapy, three were treated with a combination of radiotherapy and chemotherapy, three were treated with enucleation, and three were treated with ophthalmectomy with adjuvant radiation. Distant metastases were found in nine patients, and seven died of the disease. The time interval between detecting iris metastases and death from the disease ranged from 3 to 13mo. Unfortunately, some reported cases were lost to follow-up. Consequently, we could not determine whether there was a relationship between treatment and prognosis. Therefore, iris metastasis in esophageal cancer was often accompanied by additional systemic metastasis, and the mortality rate in these patients was elevated (Table 1).

Table 1 Summary of reports describing with iris metastasis from esophagus cancer

Author/y	Age/ sex	Eye	Presentation			Iris metastasis		History of primary cancer	Other sites of metastasis	Treatment of iris metastasis	Outcome	Interval iris metastasis to death
			Symptoms	Visual acuity	IOP (mm Hg)	Iris appearance and size	Pathologic findings					
Liu[10]/2022	67/M	Right	Blurred vision, ocular pain	20/100	13.4	Snowflakes-like deposit and iris thickening	Atypical cells	Esophageal squamous cell carcinoma	Right lung, liver, pancreas, lymph nodes	Chemoradiotherapy	Died of disease	4.5mo
Dhaka[11]/2012	53/M	Left	Headache, decreased vision	20/100	Normal	Cystic thickening of the iris stroma	NA	Esophageal adenocarcinoma	None	Stereotactic body radiation therapy and adjuvant intravitreal chemotherapy	Iris metastasis totally regressed and vision improved	NA
Wang[12]/2015	58/M	Left	Ocular pain, vision loss	20/40	10	Mass with neovascularization	Squamous cell carcinoma	Thyroid nodule	Head, stomach, lymph nodes	Local excision	Died of disease	3mo
Li[13]/2010	61/M	Right	Ocular pain, vision loss, progressive dysphagia	FC/10 cm	41	Grey mass on surface of iris, vitreous opacity	Mucoepidermoid carcinoma	Esophageal squamous cell carcinoma	NA	Enucleation	NA	NA
Lee[14]/2007	47/M	Left	A progressively enlarging red spot	20/25	Normal	A large pink, vascularized iris lesion involving the temporal pupillary margin	Neoplastic glandular epithelium consistent with metastatic adenocarcinoma	Esophageal adenocarcinoma	None	Systemic chemotherapy	NA	NA
Das[15]/2016	48/M	Left	Blurred vision	20/30	Normal	Ill-defined margins measuring 6×4×1 mm^3	Mucous secreting adenocarcinoma	Esophageal adenocarcinoma	Left cervical lymph nodes	EBRT	Died of disease	13mo
	53/M	Left	Ocular pain, blurred vision	20/100	15	Diffuse iris infiltration with 12×5×2.7 mm^3	NA	Esophageal carcinoma with regional lymph node involvement	NA	SBRT	Died of disease	12mo
	65/M	Right	Hyphema	20/40	31	Multinodular iris mass measuring 4×3×2 mm^3 with intrinsic vessels	Poorly differentiated metastatic carcinoma	Adenocarcinoma	Metastases to the left supraclavicular lymph node and bone	Radioactive plaque	Died of disease	5mo
Dobbins[16]/2009	77/M	Right	Ocular pain, foreign body sensation	20/30	Normal	2+ cells in the anterior chamber and a small peripheral amelanotic iris mass	NA	Gastroesophageal	Pulmonary	Chemotherapy	Died of disease	8mo
Lv[17]/2015	64/M	Right	Ocular pain, blurred vision	20/400	25	Gray, irregular and vascularized neoplasm with 7×5×3 mm^3	Squamous cell cancer	Esophageal squamous cell cancer, gastric stromal tumor	NA	Ophthalmectomy and adjuvant radiation	NA	NA
Ozawa[18]/2021	70/M	Right	Redness, discomfort	20/50	Normal	A yellowish-white mass with neovascularization from 4 to 7 o'clock in the anterior chamber	Squamous cell carcinoma	Esophageal cancer	Hypopharynx, lung, mediastinal and abdominal lymph glands, brain, dermis, and left thumb	Radiation therapy, chemotherapy	Died of disease	9mo
Tatai[19]/2015	75/M	Left	Ocular pain	NA	NA	A tumor on the surface of iris at 3 o'clock	NA	None	Liver and lymph node	Radiotherapy	Tumor reduced in size and pain alleviated	NA
Ichiki[20]/2005	58/M	Right	A white nodule	Normal vision	Normal	A white nodule in iris	Squamous cell carcinoma	None	Lymph node near the para-aortic region	Chemoradiotherapy	Iris metastasis disappeared and esophagus tumor size decreased	11mo
Present case	59/M	Right	Ocular pain	20/30	21	A pinkish, vascularized neoplasm located on the temporal iris expanding 6- to 9-clock	Squamous cell carcinoma	Esophageal squamous cell carcinoma	Brain	Enucleation, radiotherapy	Died of disease	12mo

NA: Not available; FC: Finger counting; IOP: Intraocular pressure.

Summary of the Cases of Iris Metastasis of Lung Cancer

Among the patients with iris metastases of lung carcinoma (Table 2)[9,21-38], 14 were men (70%), and 6 were women (30%). The mean age at diagnosis was 60.3y (range, 43–81y). The mean age of the men and women was 60.6y (50–79y) and 59.5y (43–81y), respectively. Of the 20 patients, the right eye was affected in 14 patients (70%), the left eye was affected in 5 patients (25%), and both eyes were affected in 1 patient (5%). Ocular pain was the most common complaint in patients with iris metastasis (7, 35%). Other complaints included blurred vision (6, 30%), redness (4, 20%), and development of a mass (2, 10%). The masses were white in three eyes (15%), red-orange in one eye (5%), gray in four eyes (20%), yellow in one eye (5%), translucent in two eyes (10%), pink in five eyes (25%), and unknown in four eyes (20%). Further, the masses were temporal in seven eyes (35%), superior in two eyes (10%), nasal in four eyes (20%), inferior in three eyes (15%), and diffuse in one eye (5%). Information on the IOP was described in 16 eyes. Of these, 55% had elevated IOP (>21 mm Hg), with an average pressure of 31.7 mm Hg (22–47 mm Hg), and 25% had normal IOP.

Histopathological examination and clinical features contribute to the diagnosis of iris metastasis. Nine cases (45%) were diagnosed by histopathology, including fine-needle aspiration biopsy (FNAB) in three cases (15%), iris biopsy in four cases (20%), and tissue histopathology after iris resection or eyeball removal in one case (5%). Analysis of aqueous humor cells was used for diagnosis in one case (5%). Eleven cases (55%) had no histopathological findings and were diagnosed based on ophthalmic manifestations or imaging examination. Twenty percent (four cases) of the patients had no known history of systemic cancer and were first presented to the ophthalmology department for iris metastasis. However, 80% (16 patients) had a confirmed primary tumor diagnosis prior to the ophthalmology department. Five percent (one case) of the iris metastasis cases occurred before metastasis to other parts of the body, 60% (12 cases) occurred after metastasis to other body parts, and 35% (seven cases) had an unclear sequence.

Regarding treatment, 9 (45%) patients received local treatment, 10 (50%) received systemic treatment for iris metastasis, and 1 (5%) was observed without any treatment. Local treatment included photodynamic therapy (PDT) in one case (5%), radiotherapy in three (15%) cases, intraocular injection of monoclonal antibodies in four (20%) cases, and intraocular injection of monoclonal antibodies with radiotherapy in one (5%) case. Regarding systemic therapy, four patients (20%) were treated with chemotherapy, one (5%) was treated with chemoradiotherapy, one (5%) was treated with eyeball removal with chemotherapy, two (10%) were treated with intraocular injection of monoclonal antibodies with chemotherapy, one (5%) was treated with topical antiglaucoma medications. The treatment effects were reported in 16 patients. Four (20%) cases were completely resolved, nine (45%) were partially resolved, two (10%) remained unchanged, and one (5%) case recurred. Unfortunately, six patients eventually died of the disease.

Table 2 Comparison of features of iris metastasis from esophageal cancer and lung cancer *n* (%)

Parameters	Iris metastasis from	
	Esophagus cancer (*n*=14)	Lung cancer (*n*=20)
Age at metastasis diagnosis	61.07	60.3
Sex (male/female)	14/0 (100/0)	14/6 (70/30)
Right/left/both eyes	7/7/0 (50/50/0)	14/5/1 (70/25/5)
Presenting symptoms		
Blurred vision	2 (14)	6 (30)
Ocular Pain	6 (42)	7 (35)
Mass	2 (14)	2 (10)
Redness	1 (7)	4 (20)
Foreign body sensation	1 (7)	0
Tumor color		
White	1 (7)	3 (15)
Red-orange	0	1 (5)
Grey	2 (14)	4 (20)
Pink	2 (14)	5 (25)
Yellow	1 (7)	1 (5)
Translucent	1 (7)	2 (10)
Tumor quadrant location		
Temporal	3 (21)	7 (35)
Nasal	0	4 (20)
Superior	0	2 (10)
Inferior	1 (7)	3 (15)
Diffuse	1 (7)	1 (5)
Intraocular pressure		
Increased	4 (28)	11 (55)
Mean (mm Hg)	22.3	31.7
Normal	9 (64)	5 (25)
Diagnostic approach		
Histopathology	11 (78)	9 (45)
FNAB	5 (35)	3 (15)
Iris biopsy	2 (14)	4 (20)
Histopathology after surgery or enucleation	4 (28)	1 (5)
Aqueous humor test	0	1 (5)
Nonpathological diagnosis	3 (21)	11 (55)
Detection of iris metastasis in relation to primary tumor		
Before primary tumor detection	8 (57)	4 (20)
After primary tumor detection	6 (43)	16 (80)
Detection of iris metastasis in relation to systemic metastasis		
Before systemic metastasis	8 (57)	1 (5)
After systemic metastasis	2 (14)	12 (60)
No systemic metastasis	4 (29)	7 (35)
Treatment		
Chemotherapy	4 (28)	4 (20)
Radiotherapy, chemotherapy	1 (7)	1 (5)
PDT	0	1 (5)
Radiotherapy	7 (50)	3 (15)
Intraocular injection of monoclonal antibodies	1 (7)	4 (20)
Intraocular injection of monoclonal antibodies with chemotherapy	0	2 (10)
Intraocular injection of monoclonal antibodies with radiotherapy	0	1 (5)
Local excision	1 (7)	0
Enucleation with chemotherapy	2 (14)	1 (5)
Topical antiglaucoma medications	0	1 (5)
Observation	0	1 (5)
Response to treatment		
Complete regression	2 (14)	4 (20)
Partial regression	1 (7)	9 (45)
No change	0	2 (10)
Tumor recurrence after treatment	0	1 (5)
Died of disease	8 (57)	6 (30)

FNAB: Fine-needle aspiration biopsy; PDT: Photodynamic therapy.

Table 3 Summary of clinical characteristics of patients with lung cancer metastasis and esophageal cancer metastasis

Parameters	Lung cancer metastasis	Esophageal cancer metastasis
Sex distribution	Male dominance	Male dominance
Tumor Spread	Direct diffusion metastasis, blood metastasis, and lymphatic metastasis	Direct diffusion metastasis, blood metastasis, and lymphatic metastasis
Metastatic sites	Contralateral lung, the brain, liver, adrenal glands, and bone	Spreads within the thorax, abdomen, liver, and peritoneum
Mortality	High	High
Pathological classification	Small-cell lung cancer, none small-cell lung cancer	Squamous cell carcinoma, esophageal adenocarcinoma
Risk factors	Smoking, chronic obstructive pulmonary disease, fatigue, anorexia, weight loss	Smoking, alcohol, obesity, gastroesophageal reflux disease, and Barrett esophagus
Screening	Enhanced CT, PET/CT, brain MRI	Endoscopic ultrasonography, PET/CT, chest and abdominal enhanced CT
Detection of metastasis	Distal metastatic biopsy	Biomarker testing

MRI: Magnetic resonance imaging; CT: Computed tomography; PET/CT: Positron emission tomography-computed tomography.

Comparison between Iris Metastases from Esophageal and Lung Cancer In all the cases we considered in this study, all patients with iris metastasis originating from esophageal cancer were male, and 70% of patients with iris metastasis from lung cancer were male. This suggests that male patients account for most iris metastasis cases overall. Symptoms of ocular pain and blurred vision were evident in the majority of the cases. There were no significant differences in tumor color or main location of iris metastases in both groups. Histopathological examination was the main diagnostic approach and showed 78% metastasis had occurred in esophageal cancer cases and 45% metastasis in lung cancer cases. Iris metastases were discovered prior to the primary tumor in 57% of patients with esophageal cancer and 20% of patients with lung cancer. Fifty percent of cases with iris metastases from esophageal cancer received radiation therapy, while chemotherapy and intraocular monoclonal antibodies accounted for most treatment modalities (40% in total) in cases of iris metastases from lung cancer. Of all the cases where iris metastasis was found, the mortality rate was 57% for patients with esophageal cancer and 30% for patients with lung (Table 3).

DISCUSSION

Frequency Epidemiology and Characteristics of Iris Metastasis The uveal tract is the most common site of intraocular metastases, whereas others rarely arise in the retina, vitreous humor, and optic nerve. Approximately 90% of uveal metastases involve the choroid, and the iris and ciliary body are involved in the remaining 10% of cases[8]. Uveal metastasis is the most common type of intraocular malignancy[39]. In patients with uveal metastases, 67% of cases had a known primary focus, and 33% presented no known primary cancer, which indicated that intraocular neoplasm might be the initial sign of systemic disease[8]. Breast cancer (33%), lung cancer (27%), skin melanoma (12%), kidney cancer (7%) and esophageal cancer (3%) were the most common primary cancer sites in patients with iris metastases[7]. Although systemic evaluation is relatively common, up to 15% of cases have no primary lesions[8].

Iris metastases have occasionally been clinically reported. They usually present as single or multiple white, yellow, or pink lesions or snowflakes on the surface of the iris. Iris involvement may cause pupil displacement, vasodilation, surface neovascularization, and intraocular hypertension[20]. Shields *et al*[40] followed 104 cases of metastatic iris tumors in the eye and found that ocular pain was the most common complaint (32%) of patients with iris metastasis, and the esophagus was the primary source of cancer in only three cases over 40y. Intraocular metastatic cancer is mostly blood-transmitted due to the absence of lymphatic vessels in the intraocular tissue. The most common sites are the vessel-rich uvea, particularly in choroidal metastases. The ophthalmic branch of the internal carotid artery is located at a right angle, giving cancer cells less opportunity to pass through the blood into the eye. Thus, tumor cells typically reach the choroid via the posterior ciliary artery. The choroid tissue has abundant blood vessels and moderate blood flow, suitable for tumor cells to remain and grow, and the diameter of the short posterior ciliary artery that supplies the choroid is larger than that of the long posterior ciliary artery. Consequently, intraocular metastases are mostly located in the choroid but rarely reach the iris[7].

Characteristics and Metastasis of Esophageal Carcinoma Among the leading causes of cancer-related deaths around the world, esophageal cancer ranked in the top seven, and in the top four in China[41]. Nearly half a million individuals are diagnosed worldwide each year. Esophageal cancer is a relatively aggressive malignancy of the gastrointestinal tract. Cause esophageal malignancies are often asymptomatic, they are diagnosed late in the disease course, resulting in a poor prognosis for patients. More than half of the patients present with distant metastases or unresectable disease[42]. Esophageal cancer has the lowest 5-year survival rate among all cancer types, with a rate of 40.1% in China[43]. Primary esophageal cancer is classified into two histological types: esophageal squamous cell carcinoma and esophageal adenocarcinoma[44]. Esophageal squamous cell carcinoma, the most common type worldwide, accounts for over 90% of patients diagnosed with esophageal cancer in China[45]. Most patients with early-stage esophageal cancer do not show symptoms until they develop dysphagia and weight loss, which may indicate advanced-stage

tumors. The most common site of metastasis in esophageal cancer depends on tumor histology. Esophageal squamous cell carcinoma spreads within the thorax, whereas esophageal adenocarcinoma tends to spread to the abdomen, liver, and peritoneum. It may also affect the thoracic and adrenal glands[46]. Iris metastasis in esophageal cancer is rare. In this case, a systemic imaging examination revealed the high uptake of FDG in the middle esophageal wall. Therefore, esophageal cancer was highly suspected, and a histopathological examination of the eyeball and esophagus confirmed the origin of the iris metastasis from the esophagus.

Comparison Between Iris Metastases from Esophageal and Lung Cancer Although local and systemic treatment can alleviate the symptoms and signs of iris metastasis, the mortality rate of patients is relatively high. We found that the mortality rate of iris metastasis from esophageal sources was approximately 57%, while that of iris metastasis from lung sources was approximately 30%. The reasons for the different mortality rates may be related to different types of primary tumors and the number of other metastatic sites. Among all types of cancer, 5-year survival rate for esophageal cancer remains the lowest[43]. However, the mortality rate of lung cancer is gradually decreasing, with the medical practices related to early cancer screening or treatment[42].

The gender distribution of patients with iris metastasis from lung and esophageal cancer was consistent, with metastases being more common in males. This may be related to the more frequent smoking in males, which is a common risk factor for both lung and esophageal cancer[47]. With regard to the sex of the patients, Welch *et al*[48] founded that the majority of the 1111 patients who developed uveal metastases were female (64%) and most uveal metastases originate from breast cancer. While our study found a predominance of male patients with iris metastases. This may be related to the primary site of the tumor. It is worth noting that breast cancer is predominantly found in females, while esophageal and lung cancer are more common in men.

Our study shows that males are more susceptible to iris metastasis in both cancer types. It may be due to differences in serum biomarkers between males and females. Literature revealed that there were differences in serum markers between patients with intraocular and non-intraocular metastasis of malignant tumors during serological examination, including cytokeratin fragment 19 antigen 21-1, neuron-specific enolase, alpha fetoprotein, carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 153, carbohydrate antigen 199, alkaline phosphatase, hemoglobin, and calcium[49]. The difference in serum biomarkers may be one of the risk factors for iris metastasis in male patients with esophageal cancer and lung cancer.

There was no significant difference in the clinical features of iris metastasis from these two primary tumors, and our statistical results were like those reported by Shields *et al*[40]. The main patient complaints were blurred vision and ocular pain. Blurred vision may be due to blockage of the refracting media. However, the possible causes of ocular pain are more varied, including compression of the anterior chamber angle, iris adhesions caused by anterior chamber inflammation, infiltration of tumor and inflammatory cells into the anterior chamber angle–which could obstruct trabecular meshwork–and ocular hypertension. A slit lamp examination of the iris showed predominantly gray-white masses. In both groups, histopathological examination was crucial in diagnosing iris metastasis.

Both lung cancer and esophageal cancer are highly metastatic, high mortality rate and male patients predominate. More than half of patients have metastatic disease at the time of diagnosis. Metastasis of the two cancers mainly include direct diffusion metastasis, blood metastasis and lymphatic metastasis, which is an important factor affecting their prognosis[50]. Lung cancer usually metastasize to the contralateral lung, the brain, liver, bone, and distant lymph nodes, but also to many other organs with a lower frequency[51]. The most common site of metastasis in esophageal cancer depends on tumor histology. Esophageal squamous cell carcinoma spreads within the thorax, whereas esophageal adenocarcinoma tends to spread to the abdomen, liver, and peritoneum. Smoking, and chronic obstructive pulmonary disease are the most common risk factors for lung cancer. Patients with lung cancer who have comorbid conditions such as fatigue, anorexia and weight loss are more likely to develop distant metastases. Obesity, gastroesophageal reflux disease and Barrett's esophagus are the main risk factors for esophageal adenocarcinoma[52]. Enhanced CT, PET/CT and brain MRI are commonly used to screen for lung cancer[53]. Once metastasis has occurred, biopsy of the distal metastatic site is a preferred option. Common tests for esophageal cancer include ultrasound endoscopy, PET/CT, CT and thoracic and abdominal enhanced CT. Biomarker testing play an important role in the diagnosis, classification, and molecular characterization of esophageal cancer[54].

Different sources of metastasis require further treatment. Systemic therapy is the standard for patients with stage IV non-small cell lung cancer and all small cell lung cancer[55]. Sometimes, systemic therapy must be supplemented with local treatment if a metastatic lesion is causing local symptoms[56]. This follows our results that chemotherapy and intraocular injection of monoclonal antibodies accounted for the largest proportion of patients with iris metastases from lung cancer. Once esophageal cancer is found to have metastasized distantly, treatment strategies are severely limited, and the

focus turns to relieving symptoms[57]. Among the cases of iris metastasis from esophageal cancer we included, radiation therapy accounted for the majority. This is probably because once distant metastases of esophageal cancer–such as the iris and other parts–occurred, the prognosis was poor, and radiation therapy could locally reduce the volume of the tumor and alleviate the symptoms. Thus, identifying the source of the primary tumor and providing targeted therapy may improve the overall survival rate[58]. Treatment strategies for secondary ocular malignancies depend on individual patients, including the location of the metastatic lesion, whether there are single or multiple lesions, the laterality of affected eyes, whether the lesion involves the macula or optic nerve and the overall prognosis of the patient.

Role of PET/CT, Fine Needle Aspiration Biopsy and Serological Examination It is necessary to develop appropriate tools for the early diagnosis and treatment of ocular cancers. The imaging technique is a non-invasive method for diagnosing ocular tumors and is considered equally reliable as biopsy in the diagnosis of different types of eye cancers[59-60]. Moreover, it can be used for pre-therapeutic diagnosis and pre-therapeutic monitoring of ocular tumors. The PET/CT technique can retrieve information about the size, shape, and location of the tumor by exploiting the high glucose demand of cancer cells. It tells the difference between cancerous and normal structures by using a whole-body scan to determine whether there is metastasis throughout the body[61]. In this case, whole-body PET/CT studies can successfully identify the primary site and other metastatic lesions not found on CT or MRI, thus contributing to accurate patient management[62]. A systemic examination, including CT, MRI, or PET/CT scans of the chest and abdomen, as well as serum studies for relevant cancer markers and mammography, should be performed for patients with no history of systemic malignancy. Total body CT with contrast medium represents a rapid and efficient tool for staging, and MRI represents the better imaging technique for obtaining local staging in the orbital area. PET/CT, a powerful diagnostic tool that can identify otherwise occult metastases, is crucial for avoiding unnecessary surgical intervention in patients with distant metastases[63]. PET/CT, CT, and MRI are conventional imaging modalities in initial work-up for a metastatic patient.

According to Shields *et al*[40], who have more than 40y of experience in ocular oncology and published the two largest studies on iris metastasis from systemic cancers, the best method for diagnosing iris metastasis is an observation of the typical tumor *via* slit-lamp biomicroscopy in patients with a history of malignancy. FNAB of the suspicious iris mass is the best auxiliary diagnostic method for the diagnosis of uncertainty[64]. FNAB has been successfully used for iris lesions via the clear corneal approach[65]. However, the most important limitation of this technique is the inconclusive cytopathological diagnosis due to inadequate sampling and complications, such as hemorrhage and the potential for intraocular tumor dissemination[66]. In addition, our patient could not undergo fine-needle puncture due to the large size of the iris lesion.

The identification of potential risk factors for iris metastasis of esophageal cancer has become particularly important to avoid the occurrence of such metastasis. Serological examination is a method of diagnosing tumors by detecting biomarkers in serum, which can indicate whether a tumor has metastasized to other tissues[67]. Detection of serological biomarkers can be used for early diagnosis, intervention, and treatment of iris metastasis of esophageal cancer. Early diagnosis has a better prognosis compared to late diagnosis. Early and good prognosis can effectively reduce the risk of tumor metastasis and prevent visual impairment and eye damage. This may effectively improve the quality of life of patients with esophageal cancer.

Management Management of ocular metastases includes systemic chemotherapy, immunotherapy, hormone therapy, whole-body radiotherapy, external beam radiotherapy, plaque radiotherapy, transpupillary radiotherapy, and PDT[6]. Multifactorial evaluations to determine appropriate treatment options include life expectancy, visual function, and patient expectations. Patients with additional systemic involvement should be treated with chemotherapy. External radiotherapy or brachytherapy is recommended for treating focal metastases[68]. External beam radiation therapy is usually used for extensive, multifocal, or bilateral lesions because uveal metastases are sensitive to radiation[69]. Plaque brachytherapy usually only targets a single lesion and has achieved excellent success without the need for repeated treatment[70-71]. PDT can be performed in a single session, with a success rate of over 70%, and is less invasive than radiation. It is best used for pigmented, small, and posterior lesions. After treatment, 95% of ocular metastases can be controlled without recurrence[72]. Nevertheless, the survival rate depends on the state and type of primary tumor. If local treatment is not promptly administered, metastasis may recur, leading to irreversible vision loss. Therefore, close monitoring is necessary. Enucleation is an important step in intraocular tumor treatment. It is generally used in cases of irreversible blindness and painful eyes due to persistent tumor growth and neovascular glaucoma in most cases[6]. The decision to remove the eyeball is made when the eye is irreparable. However, it was unsuitable to perform a local tissue biopsy owing to the rapid growth of iris metastases

in this patient; thus, the eye had to be enucleated to identify the primary lesion. Dhakal *et al*[11] concluded that stereotactic body radiation therapy, in combination with intravitreal chemotherapy, is an effective and well-tolerated palliative treatment for iris metastasis from esophageal cancer. Hormone therapy is a more aggressive treatment for tumors with estrogen and progesterone surface receptors, such as breast and prostate cancers[73]. It is also essential to detect the presence of brain metastases to treat such lesions with radiation, along with ocular irradiation[6].

Moreover, because the diagnosis of the primary tumor occurs after iris metastasis, life expectancy is generally poor in patients with intraocular metastases[6], below 25% at 5y[8], with an overall mean survival of 15mo, ranging from 3 to 96mo after diagnosis[4,74]. Lung carcinoid cancer had the highest 5-year survival rate, whereas pancreatic and kidney cancer showed the lowest 5-year survival rates. Large tumors and metastasis of esophageal cancer to the iris are rare in clinical practice. It has been suggested that ocular masses should be considered in clinical practice and that specialized and systemic lesions should be carefully examined to avoid misdiagnosis and missed diagnosis. Thus, understanding the various ocular manifestations of metastatic diseases will facilitate timely assessment and treatment, which is crucial for proper early diagnostic work-up to enable the identification of primary tumors to establish appropriate treatment, avoid blindness in the advanced stages of generalized tumor disease, and improve the prognosis of the patient.

In conclusion, this case indicates that esophageal carcinoma could cause isolated iris metastasis, which can be diagnosed based on clinical history, ocular examination, and systemic and histopathologic evaluation. Iris metastases can present as iridocyclitis or glaucoma. Considering the variable clinical presentation and poor prognosis of cases of esophageal cancer with iris metastasis, it is necessary to discuss each case with the group of oncologists to provide a comprehensive treatment for each patient based on the different conditions. For patients with no history of malignant tumors accompanied by iris mass and intraocular hypertension, a general examination should be conducted to identify the primary tumor, and appropriate treatment should be determined after a comprehensive evaluation to improve patients' prognoses and avoid advanced blindness and death caused by widespread tumor diseases.

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