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Case Report

Metastatic Intraocular Tumor Likely from Hepatocellular Carcinoma Mimicking Panuveitis

Eri Takasu[a], Yusuke Shiode[a]*, Hiroya Kindo[a], Shuhei Kimura[a], Mio Hosokawa[a], Ryo Matoba[a], Yuki Kanzaki[a], Tetsuro Morita[a], Takuya Adachi[b], Motoyuki Otsuka[b], and Yuki Morizane[a]

Departments of [a]Ophthalmology, of [b]Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

A 77-year-old man undergoing treatment for hepatocellular carcinoma (HCC) presented with blurred vision in his right eye, persisting for 2 months. Slit-lamp microscopy and fundus examination revealed inflammatory cells in the anterior chamber, severe vitreous opacities, and retinal vasculitis in the right eye. The patient underwent vitreous surgery with biopsy, and vitreous cytology confirmed a metastatic intraocular tumor originating from the HCC. Radiotherapy was administered to the right eye, with no recurrence of intraocular inflammation observed at 10 months post-irradiation.

Key words: metastatic intraocular tumor, hepatocellular carcinoma, panuveitis, uveitis masquerade syndrome

Metastatic intraocular tumors occur when the spread of systemic malignancies reaches the eye. The most common primary sites are the breast (37-47%), followed by the lung, gastrointestinal tract, kidney, skin, and prostate [1,2]. The choroid accounts for approximately 90% of ocular metastases, while metastases to the vitreous or retina are rare [1,2].

Hepatocellular carcinoma (HCC), the most prevalent type of primary liver cancer, is a malignant tumor capable of systemic metastasis, particularly to the lungs, lymph nodes, bones, and adrenal glands [3,4]. Reports of HCC metastasizing to the eye are uncommon, with most cases documenting choroidal masses [5,6]. Herein, we present a case of a metastatic intraocular tumor from HCC that mimicked panuveitis. This condition was initially suspected to be non-infectious uveitis, but vitreous cytology confirmed the diagnosis, and visual acuity improved following radiotherapy. This report offers critical insights into differential diagnosis and therapeutic approaches for metastatic intraocular tumors.

Case Presentation

A 77-year-old Japanese male presented with blurred vision in his right eye, persisting for 2 months. He had cataract surgery in both eyes 2 years prior. His medical history included treated hypertension, diabetes mellitus, and atrial fibrillation. He was diagnosed with HCC 9 years earlier and had undergone multiple treatments, including transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA). Histopathological examination of a liver biopsy revealed well-differentiated HCC. A metastatic lesion in the left scapula had been detected 9 months earlier and treated with radiation therapy and systemic chemotherapy using atezolizumab and bevacizumab.

Upon presentation, his best-corrected visual acuity (BCVA) was 20/400 in the right eye and 20/13 in the

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*Corresponding author. Phone: +81-86-235-7297; Fax: +81-86-222-5059
E-mail: phut4c98@okayama-u.ac.jp (Y. Shiode)

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left. Intraocular pressure was 10 mmHg in both eyes. The right eye showed no ciliary hyperemia, and the cornea was clear. There were 3+ inflammatory cells [7] in the anterior chamber and a 1-mm hypopyon (Figs. 1A and B). Inflammatory cells were also present in the anterior vitreous, and fundus visibility was poor due to 2+ vitreous opacity [7]. The optic disc appeared normal, but large retinal vessels were whitened, with hemorrhages and hard exudates noted in the temporal retina (Fig. 1C). Optical coherence tomography (OCT) showed no abnormal macular morphology, although the image was unclear (Fig. 1D). The left eye examination was unremarkable (Fig. 1E-H). No systemic symptoms, such as stomatitis, vulvar ulcers, skin lesions, or arthritis, were observed. Blood tests indicated a mildly elevated C-reactive protein (CRP) concentration of 0.49 mg/dl, with no other inflammatory signs. Serological tests were positive for hepatitis B e antibody and hepatitis B core antibody, while the hepatitis B surface antigen was negative. Hepatitis B virus (HBV) DNA was undetectable, indicating a past HBV infection without current viral activity. No evidence of active infection, such as other viral hepatitis, cytomegalovirus, tuberculosis, or syphilis, was found.

Initially, panuveitis of the right eye was suspected, and treatment with 1.5% levofloxacin and 0.1% betamethasone eye drops was initiated. However, the inflammation did not improve, leading to vitreous surgery for diagnosis and treatment one month later. Extensive whitening of the retinal vessels and multiple retinal hemorrhages were observed after the removal of the vitreous opacity. These findings indicated occlusive

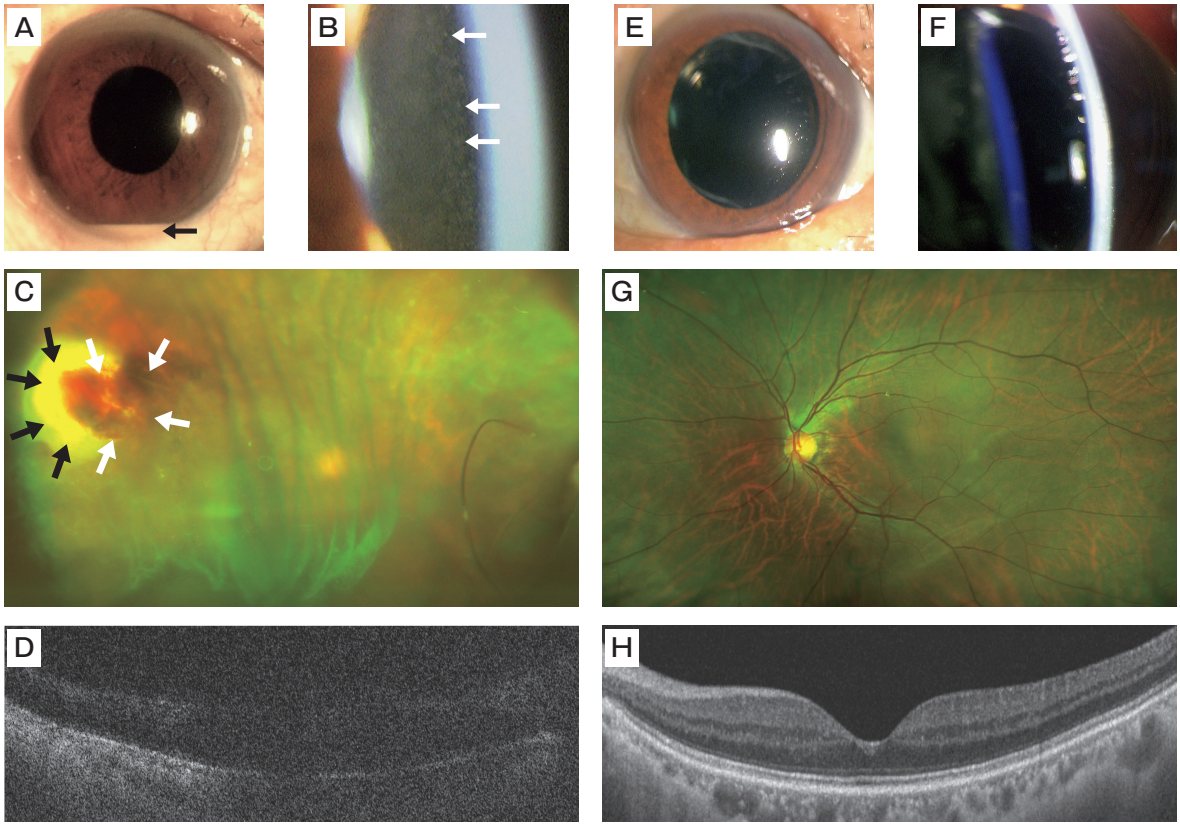

Fig. 1 Clinical findings at initial examination. Slit-lamp microscopy and fundus examination findings of the right (A-D) and left (E-H) eyes. Examination revealed a 1-mm hypopyon (arrow, A) and 3+ anterior chamber inflammatory cells (arrows, B) in the right eye. Fundus imaging was unclear due to severe vitreous opacities, showing whitening of large retinal vessels with retinal hemorrhage (white arrows, C) and hard exudates (black arrows, C) in the temporal retina. A horizontal optical coherence tomography (OCT) scan of the right macula showed no abnormal morphology, although the image was hazy (D). The left eye showed no abnormal findings in the anterior segment (E) or inflammatory cells (F). Fundus imaging and OCT findings of the left eye were unremarkable (G and H).

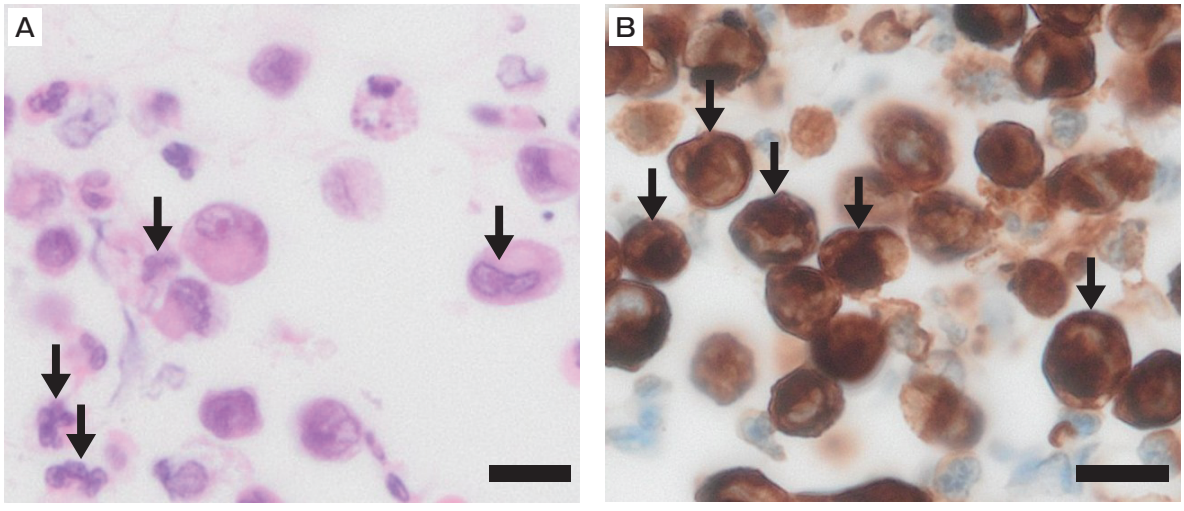

Fig. 2 Microscopic images of the vitreous cells. (**A**) Hematoxylin–eosin staining showing severe nuclear atypia (arrows), classified as Class V. Scale bar = 10 μm. (**B**) Immunostaining for Cytokeratin AE1/AE3 showing cytoplasmic staining (arrows). Scale bar = 10 μm.

retinal vasculitis, and panretinal photocoagulation was performed. No mass lesions or retinal detachments were noted. Vitreous cell cytology revealed Class V malignant cells (Fig. 2A). Immunostaining was positive for Cytokeratin AE1/AE3 (Fig. 2B), indicating an epithelial tumor. Markers of lymphoid tumors (CD20, CD3, CD79a, and CD30) and markers highly specific for HCC (hepatocyte paraffin-1, Arginase-1, and Glypican-3) were all negative. No intracytoplasmic bile pigment was found in the malignant cells. Both bacterial culture and PCR tests [8] of the vitreous humor yielded negative results.

Systemic imaging pre- and post-operatively showed no tumors other than scapular and mediastinal lymph node metastases from HCC. Consequently, a diagnosis of metastatic intraocular tumor from HCC was made, and systemic chemotherapy with durvalumab and tremelimumab was initiated.

Two weeks post-surgery, both anterior chamber and vitreous cell inflammation decreased, with improved fundus visibility. Visual acuity in the right eye recovered to 20/63. However, inflammation in the anterior chamber with hypopyon and diffuse vitreous opacification recurred 3 weeks later, leading to a decline in visual acuity to hand motion. Radiotherapy (36 Gy in 12 fractions) was administered to the right eye. One month post-radiotherapy, BCVA improved to 20/63, with resolution of both anterior chamber inflammatory cells and vitreous opacity (Fig. 3A-D). No recurrence of

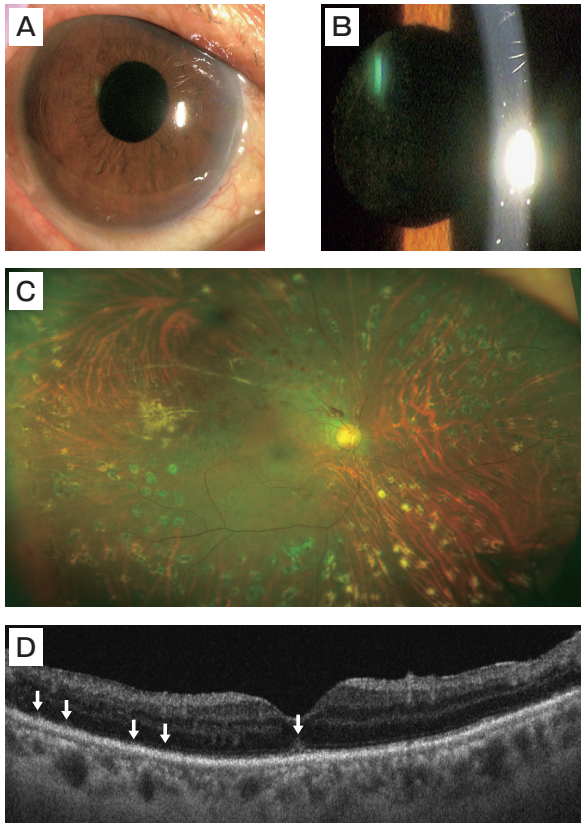

Fig. 3 Clinical findings of the right eye after radiotherapy. Slit-lamp microscopy revealed no hypopyon or inflammatory cells in the anterior chamber (**A**, **B**). Vitreous opacity resolved, and fundus visibility improved (**C**). A horizontal OCT scan of the right macula showed disruption of the outer retinal layers (arrows, **D**).

inflammation was noted during the 10-month follow-up. The left eye remained free of inflammatory findings throughout this period.

All procedures performed during the treatment of the patient adhered to the ethical standards of the Okayama University Hospital Research Committee and the Helsinki Declaration with its later amendments. Written informed consent was obtained from the patient for the publication of this case report.

Discussion

International surveys indicate that primary liver cancer is the sixth most commonly diagnosed cancer, following breast, lung, colon, prostate, and stomach cancers. It is also the third leading cause of cancer-related death [9,10]. HCC accounts for approximately 90% of primary liver cancer cases [11,12] The most frequent sites of extrahepatic metastases are the lungs, followed by lymph nodes, bones, and adrenal glands [3,4]. In contrast, ocular metastasis from HCC is extremely rare, with only 2 case reports in the literature: Wesolowski *et al.* described choroidal metastasis adjacent to the optic disc [5], and Malaviya *et al.* reported amelanotic choroidal metastasis [6]. Both cases involved choroidal mass lesions. The present case differs, as there were no detectable masses, only findings suggestive of uveitis. Long-term prognosis data for metastatic intraocular tumors from HCC are limited, making follow-up essential due to the risk of inflammation and tumor recurrence.

The patient's presentation was suggestive of uveitis, initially difficult to differentiate from noninfectious uveitis. The phenomenon in which malignancies or lymphoproliferative diseases mimic uveitis, as observed in the present case, is termed uveitis masquerade syndrome [13-15]. Conditions such as primary intraocular lymphoma [16,17], leukemia [18,19], ocular metastasis [20], and retinoblastoma [21] may present similarly. No cases of uveitis masquerade syndrome attributed to HCC have been reported. This case was non-infectious, refractory to steroid eye drops, and presented with significant vitreous opacity. In such instances, uveitis masquerade syndrome should be included in the differential diagnosis, warranting a systemic evaluation for underlying malignancy. Systemic tumors should be considered a potential cause in cases of uveitis masquerade syndrome.

The pathophysiological mechanisms by which malignant cells mimic uveitis remain unclear; however, several theories exist. Malignant cells can directly infiltrate the eye, triggering abnormal local inflammatory responses [22]. They may also produce inflammatory cytokines and chemokines [16,17,23,24], or the immune system may overreact to tumor antigens [22,25]. Additionally, angiogenic growth factors secreted by malignant cells may disrupt the blood-retinal barrier, leading to fragile neovascular vessels and inflammation [26]. Further elucidation of tumor-associated inflammatory pathways may enhance early diagnosis and management of uveitis masquerade syndrome.

This case report has two notable limitations. First, the relatively short follow-up period limits the ability to fully assess long-term prognosis or the potential recurrence of intraocular inflammation or tumor growth. Second, although malignant cells were detected in the vitreous and immunostaining was positive for Cytokeratin AE1/AE3, HCC-specific immunohistochemical markers were negative. Therefore, the diagnosis of intraocular metastasis from HCC could not be confirmed pathologically with high specificity and was based primarily on clinical history and exclusion of other primary malignancies.

In conclusion, this report presents a case of a metastatic intraocular tumor from HCC that mimicked panuveitis. Diagnosis was confirmed through vitreous cytology, and both vitreous surgery and radiotherapy proved effective. This report provides new insights into the diagnosis and treatment strategies for metastatic intraocular tumors.

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