

A Case of Intraocular Metastasis of Lung Cancer Diagnosed Using Cell Block Preparation of the Vitreous Humor

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Abstract. *Background/Aim:* Masquerade syndrome is characterized by uveitis-like manifestations caused by tumor cell infiltration into the ocular tissues. The aim of the study was to report a lung cancer patient with persistent unilateral vitreous opacity, who was eventually diagnosed with masquerade syndrome using cell block preparation. *Case Report:* An 82-year-old female complained of blurred vision in her left eye (OS). Because of pulmonary adenocarcinoma, she had previously received anticancer drug treatment at another Hospital and achieved partial remission. Ophthalmic examinations revealed anterior chamber inflammation and vitreous opacity OS. Corticosteroid eye drops were administered, but the inflammation did not improve, and was referred to the Hokkaido University Hospital. The left best-corrected visual acuity was 0.1 with normal intraocular pressure. Anterior chamber inflammation was 2+ cells, and vitreous haze was 4+ OS. B-mode ultrasonography showed diffuse heterogeneous high echoic changes in the vitreous cavity. She underwent vitrectomy, and cell block preparation of the vitreous infusion fluids was performed. Cytopathology

revealed adenocarcinoma cells with a high nuclear/cytoplasmic ratio and glandular formation. The immunocytochemical study showed that tumor cells were positive for thyroid transcription factor-1 (TTF-1), napsin A, and CK7, therefore diagnosis of masquerade syndrome due to intraocular metastasis of pulmonary adenocarcinoma was reached. Chemoradiotherapy was administered, and the eye got phthisis bulbi after irradiation 2 years after diagnosis. *Conclusion:* Cell block preparation using vitreous humor may be useful in the diagnosis and management of intraocular metastasis of pulmonary adenocarcinoma in patients with prolonged vitreous opacity.

Uveitis-like manifestations caused by tumor cell infiltration into the ocular tissues or degeneration of the vitreous are called masquerade syndrome. Various refractory disorders, such as malignant lymphoma, amyloidosis, and metastatic tumors, are likely to cause masquerade syndrome; however, those lesions could be misdiagnosed to benign inflammatory lesions. Reports of masquerade syndrome due to lung cancer are extremely rare, and its frequency is thought to be about 0.1% of all uveitis (1). Although Tan *et al.* identified lung cancer cells with vitrectomy cytology (2), there are no reports obtaining clear pathological pictures and immunocytochemical studies are not available. We, herein, report a patient with pulmonary adenocarcinoma presenting with persistent unilateral vitreous opacity, who was eventually diagnosed with masquerade syndrome using cell block preparation.

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Key Words: Lung adenocarcinoma, vitreous, cell block preparation, cytopathology, immunocytochemistry.

Case Report

An 82-year-old woman became aware of vision loss in her left eye (OS) around April 2019. She had a medical history of pulmonary adenocarcinoma, which showed partial remission under pembrolizumab administration in October 2019. She visited an ophthalmology clinic with a chief complaint of vision loss OS in May 2019. The best-corrected

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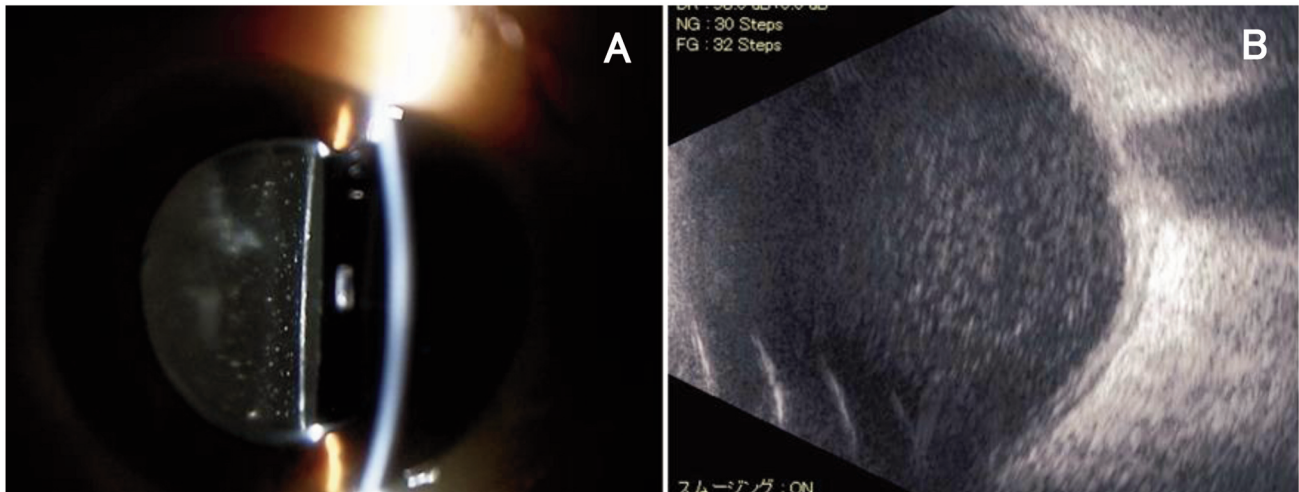


Figure 1. Ocular findings. (A) Slit-lamp microscopic image revealed anterior vitreous cells. (B) B-mode ultrasonography showed diffuse high echoic changes in the vitreous.

visual acuity (BCVA) was 0.2 OS. There was anterior chamber inflammation showing 1+ cells and 2+ diffuse vitreous haze OS. Betamethasone eye drops (0.1%) were prescribed 4 times per day OS, but the inflammation and vitreous haze did not improve. She was referred to the Hokkaido University Hospital for further examination and managements 5 months later.

At the initial visit, best corrected visual acuity (BCVA) was 0.8 on the right eye (OD), and 0.1 OS. Intraocular pressure (IOP) was 13 mmHg OD, and 19 mmHg OS. There was no inflammation OD, while anterior chamber inflammation with 1+ flare and 2+ cells (indicating moderate inflammation) was observed OS. Both eyes were pseudophakic. There was a marked 4+ vitreous haze; therefore, ocular fundus could not be seen OS. B-mode ultrasonography showed diffuse heterogeneous high echoic changes in the vitreous (Figure 1). No inflammatory findings were observed, while fundus revealed laser scars at the upper quadrant and mild cord-like vitreous opacity OD.

In October of 2019, she underwent pars plana vitrectomy (PPV) OS. Intraoperative observations included: whitening of nasal retinal vessels and mild color change in the retina without retinal hemorrhage, neovascularization, or retinal detachment. Cell block preparation using the vitreous infusion fluids was conducted according to a previous report (3, 4). Hematoxylin and eosin (H&E) staining of cell block cytology showed a variety of tumor cells with high nuclear/cytoplasmic ratio and glandular formation (Figure 2). Through immunostaining, tumor cells were positive for cytokeratin (CK) 7, an epithelial cell marker, and negative for CK20. Cells were also positive for transcription factor-1 (TTF-1) and napsin A, markers of pulmonary adenocarcinoma (Figure 3). Based on the results of cell

block preparation, she was diagnosed with masquerade syndrome due to intraocular metastasis of pulmonary adenocarcinoma.

After the PPV, corneal edema appeared and progressed, and visual acuity dropped to hand motion OS. Anterior chamber inflammation and vitreous haze remained unchanged OS. A systemic examination revealed brain metastasis of the tumor. Therefore, external-beam radiation (60 Gy/30 Fr) was administered to the left eye and brain, and adjuvant nivolumab was given intravenously (5 times in total). After irradiation, the left eye became phthisis bulbi possibly caused by the impairment of ciliary body function. Two years after the initial diagnosis, the patient was still alive and visual acuity remained hand motion OS.

Cell block preparation, cell block cytology and cell block immunostaining. For pathological analysis, cell block preparation was performed as follows: Vitreous perfusion fluid obtained at the end of vitrectomy was centrifuged at $3,000 \times g$ for 3 min and the supernatant was discarded. The dry pellet was fixed in 10% neutral buffered formalin overnight, and then the samples underwent standard processing for paraffin embedding and five-micrometer unstained sections were made. H&E staining and immunocytochemical staining were then performed (4, 5). Immunocytochemical staining was performed in an automatic immunostainer (Ventana Medical Systems, Tucson, Arizona, USA) using antibodies against CK7 (clone SP52) (Roche, RTU, Mannheim, Germany), CK20 (Clone SP33) (Roche), TTF-1 (clone 8G7G3/1) (DAKO, Carpinteria, CA, USA), Napsin A (clone TMU-Ad02) (IBL, Fujioka, Japan).

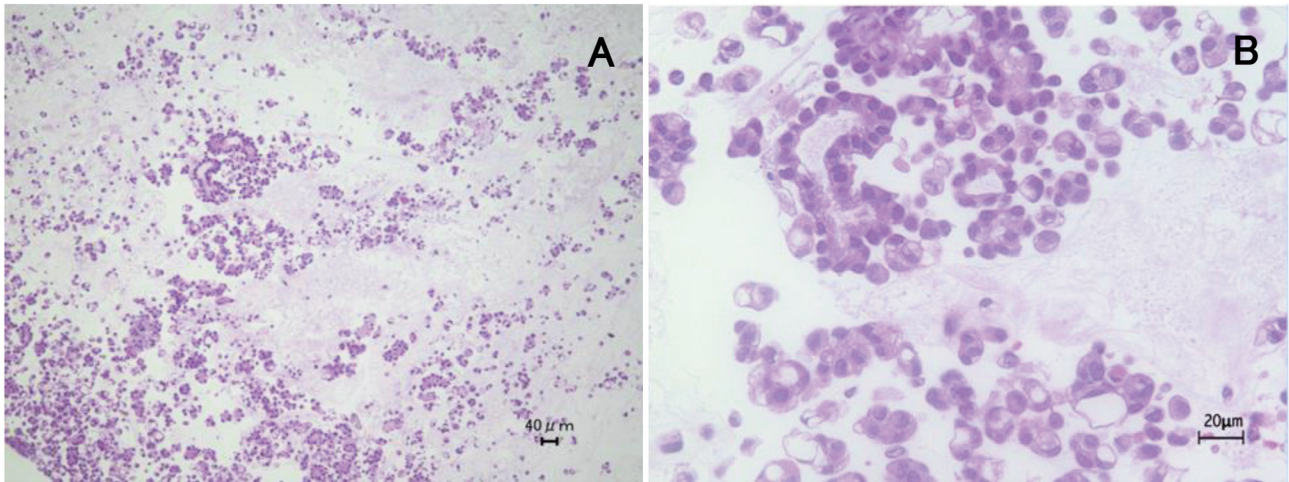


Figure 2. Hematoxylin-Eosin (H&E) staining in the vitreous cytology. (A) Low-power field image showing hyper cellularity. Numerous cellular components and mucus-like material were observed. (B) Adenocarcinoma cells with a high nucleus/cytoplasmic ratio can be seen under various glandular formations.

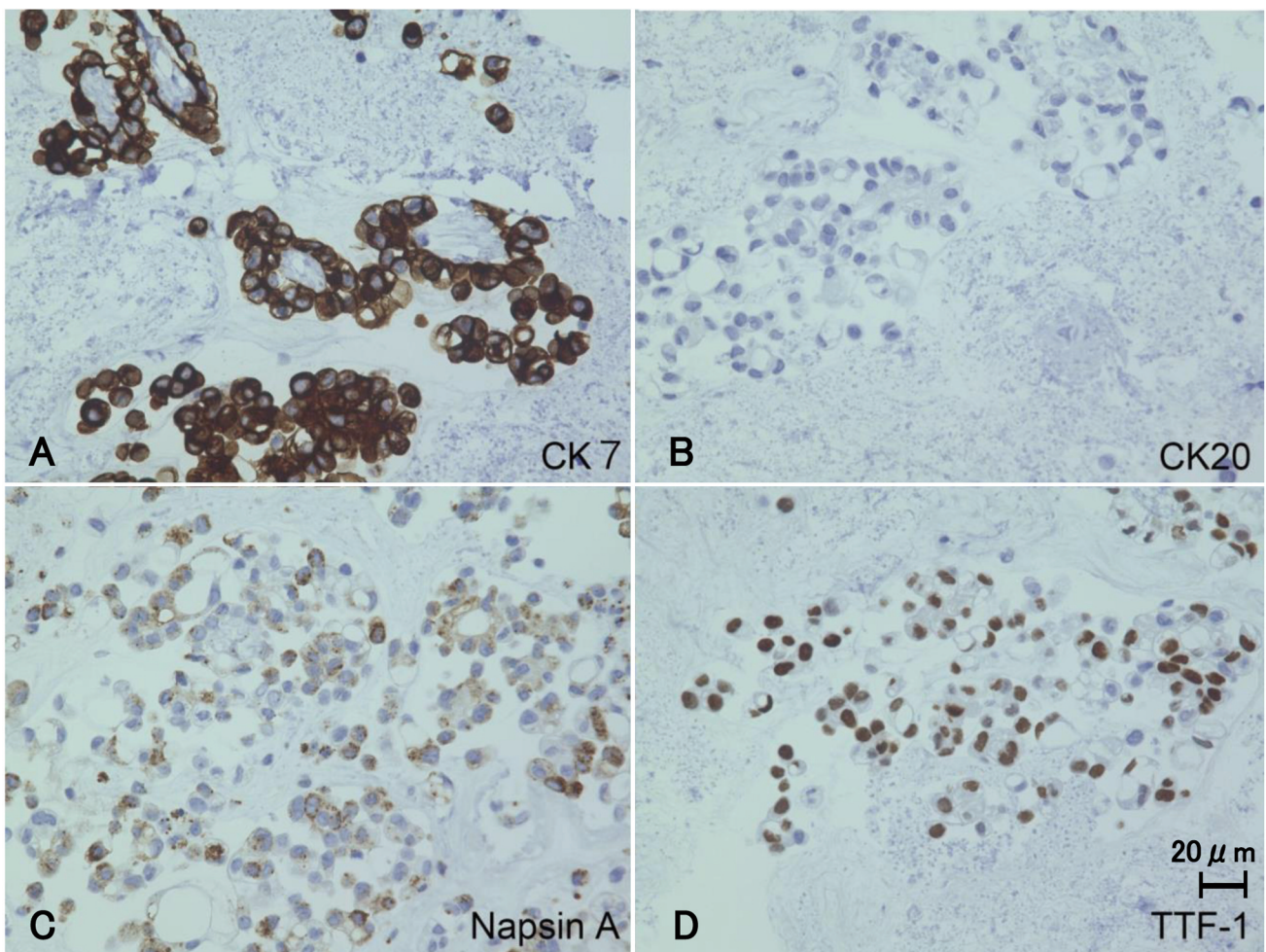


Figure 3. Immunocytochemical examination of vitreous cell block preparations. Tumor cells were positive for CK7 (A) and negative for CK20 (B). Cytoplasmic and nuclear immunoreactivity for napsin A (C) and TTF-1 (D), respectively, can be clearly observed.

Discussion

With regard to the epidemiology of metastatic tumors, an epidemiologic study of 5,378 uveitis patients showed that malignant tumors accounted for 2.6% of all uveitis cases, and metastatic tumors accounted for 5.7% of malignant tumors (6). Based on this evidence, masquerade syndrome caused by metastatic tumors is considered a rare manifestation. In a study of 80 patients who underwent PPV/choroidal biopsy due to the differential diagnosis of intraocular lymphoma, 14% and 74% of patients were diagnosed as malignant lymphoma and reactive cellular infiltrate, respectively (7). Although conventional smear vitreous cytology with PPV is useful for definitive diagnosis of intraocular lymphoma, its positivity rate is not high. On the other hand, we demonstrated that cell block preparations using vitreous infusion fluids contributed to better detection of intraocular lymphoma cells (3, 4, 8). It is indisputable that early detection of malignant cells is important to facilitate prompt treatments in case of intraocular metastasis; therefore, cell block cytology may be helpful for diagnosis in prolonged vitreous haze.

Tan *et al.* reported a case of masquerade syndrome due to pulmonary adenocarcinoma, presenting with snowball vitreous opacities, Roth spots, and drusen in a 73-year-old male (2). Chest imaging revealed abnormalities consistent with pulmonary adenocarcinoma, and the ophthalmic lesion was diagnosed as masquerade syndrome. Although the authors stated that vitrectomy proved the presence of adenocarcinoma cells, the detailed vitreous cytology was not clearly described (2). In this study, we were able to clearly identify adenocarcinoma cells with obvious glandular formation, and immunocytochemical work-up was possible at the same time by means of vitreous cell block preparations.

In general, the average survival period after diagnosis of choroidal metastasis are 7 months. Breast (47%) is the most common primary site of the metastasis, followed by lung (21%) and then the intestine (4%) (9). Radiation therapy is the most common treatment option for metastatic lung and breast cancer, and is able to stabilize or improve vision in about 80% of patients (9). In this case, radiation therapy was also employed, and eventually saved the patient life 2 years after the diagnosis of intraocular metastasis, although the eye got phthisis bulbi with poor vision.

In this case, the severe inflammatory reaction occurred during pembrolizumab administration. Therefore, it should be necessary to rule out immune-related adverse events (irAE) caused by immune checkpoint inhibitors (ICI), which have become increasingly popular among ophthalmologists in recent years. ICI initially bind to immune checkpoint molecules or their ligands, then inhibit immunosuppressive signals, and release the tumor suppressors through T cell activation, which leads to cellular attack by T cells towards

tumor cells. On the other hand, the risk of autoimmune side-effects is a major concern. ICI can also cause adverse effects in ocular tissue, such as uveitis (1%) and dry eye (1% to 24%), which are often identified within weeks or months from the start of administration (10). In this case, since the cause was diagnosed as metastasis, there was no need to stop ICI, but in general, if uveitis associated with irAE is observed during ICI use, the administration should be suspended (11).

Conclusion

In this case report of prolonged vitreous opacity, cell block preparations using vitreous infusion fluids proved useful towards the diagnosis of intraocular metastasis from pulmonary adenocarcinoma. Cell block preparations can provide a clear picture of cytological morphology, as well as immunocytochemical phenotypes in the vitreous, therefore can facilitate a treatment plan, and preserve the life of the patient.

Conflicts of Interest

Susumu Ishida has received research funding from Santen pharmaceutical CO., LTD regarding other topics, such as retinal disorders, which are not related to this study.

Authors' Contributions

KM wrote the manuscript and made substantial contributions to the conception of the work. SK critically revised manuscript and obtained pathological photographs. KN operated on the patient and revised the manuscript. YM critically evaluated the pathological findings and revised the pathological findings. DI, YM and SI were involved in manuscript preparation and reviewing. All Authors read and approved the final manuscript.

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