

Received: 2015.05.08
Accepted: 2015.07.15
Published: 2015.10.13

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 728-732
DOI: 10.12659/AJCR.894600

Effective Treatment with Intravitreal Injection of Bevacizumab for Exudative Retinal Detachment Secondary to Choroidal Metastasis of Non-Small Cell Lung Carcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDEF 1 **Hirotohi Yasui**
ABCDEFG 1 **Kazuhide Sato**
DE 1 **Yoshihiro Takeyama**
BD 2 **Hiroaki Nishihara**
BD 3 **Matsuyoshi Maeda**
EG 1 **Hideo Gonda**
EG 1 **Ryujiro Suzuki**

1 Department of Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi-shi, Japan
2 Department of Ophthalmology, Toyohashi Municipal Hospital, Toyohashi-shi, Japan
3 Department of Clinical Pathology, Toyohashi Municipal Hospital, Toyohashi-shi, Japan

Corresponding Author: Kazuhide Sato, e-mail: kazuhydesato@yahoo.co.jp
Conflict of interest: None declared
Source of support: This work was supported by CJLSG (Central Japan Lung Study Group)

Patient: Male, 68
Final Diagnosis: Non-small cell lung cancer
Symptoms: —
Medication: —
Clinical Procedure: TBLB • PET • OCT • fluorescence angiography
Specialty: Oncology

Objective: Challenging differential diagnosis





Background: Visual disturbance caused by cancer metastasis from other organs is one of the largest challenges to cancer patients' quality of life (QOL). Lung cancer is the most frequent primary site of choroidal metastasis in men, but improvement of visual disturbance has not always been emphasized in lung cancers. Recently intravitreal bevacizumab is a newer modality being tried for local control of choroidal metastases.

Case Report: A 68-year-old man was admitted the hospital with complaint of visual disturbance in his left eye. He was diagnosed with lung adenocarcinoma cT2N0M1b (OSS, OTH) stage IV. The ophthalmologic evaluation showed exudative fluid, which caused retinal detachment under the retina. Fluorescence angiography showed granular hyperfluorescence with leakage consistent with a tumor. He received radiotherapy for bone metastasis and systematic chemotherapy with carboplatin, pemetrexed, and bevacizumab, as well as intravitreal injection of bevacizumab 1.25 mg to improve the visual disturbance. His visual symptom and retinal detachment improved until he died. An autopsy revealed that the metastatic lesion in his left eye was totally cured macroscopically and microscopically.

Conclusions: We report a case of exudative retinal detachment secondary to a metastatic choroidal tumor from lung adenocarcinoma, which was treated with chemotherapy and intravitreal injection of bevacizumab. Although he finally died of lung cancer, he maintained his visual QOL and autopsy revealed complete cure of the choroidal metastasis.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Choroid Diseases • Intravitreal Injections • Vascular Endothelial Growth Factor, Endocrine-Gland-Derived

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/894600>

 1373   2  21



Background

Choroidal metastasis is the most common type of intraocular malignancy. The most common primary sites associated with choroidal metastasis are breast cancer in women and lung cancer in men [1]. Recent improvements in cancer therapy have lengthened patient survival times and improved the detection rate [2]. Although symptomatic choroidal metastasis is less common than asymptomatic choroidal metastasis, visual disturbance due to cancer metastasis from other organs is one of the most important limits to cancer patients' quality of life (QOL) [3,4]. Therefore, further improvement of the therapy for visual disturbance is needed. Clinically available therapies for choroidal metastasis are currently very limited and include systemic chemotherapy, external beam radiotherapy (ERBT), radioactive plaque therapy, and enucleation. In addition, transpupillary thermotherapy and photodynamic therapy (PDT) have been done [3]. For tumor lesions that are larger than 4-disc diameter with retinal detachment, radiotherapy or chemotherapy is used [5]. Chemotherapy causes systemic adverse effects and is not always effective [6]. Radiotherapy enables local therapy, but has several complications, including cataract, exposure keratopathy, iris neovascularization, radiation retinopathy, and radiation papillopathy [1]. Moreover, these therapies are usually long-term.

Intravitreal bevacizumab is a newer modality being tried for local control of choroidal metastasis. Bevacizumab, a monoclonal antibody targeting vascular epithelial growth factor (anti-VEGF), has recently been used in the treatment of cancer to inhibit tumor growth by blocking angiogenesis [7]. Since metastasis occurs through blood circulation and colonization to distant sites, cancer angiogenesis plays an important role. Thus, anti-cancer angiogenesis therapy is suitable for metastatic lesions [7,8]. Additionally, if it is used with intravitreal injection, high-dose bevacizumab can cure the metastasis lesions [6,9]. To date, 9 reports involving 11 cases have been published on intravitreal bevacizumab as a primary treatment modality for choroidal metastasis from lung cancer [1,10,11]. Herein, we report a case of effective treatment with intravitreal injection of Bevacizumab for exudative retinal detachment secondary to choroidal metastasis of non-small cell carcinoma (NSCLC).

Case Report

A 68-year-old man attended an eye clinic with complaint of visual disturbance in the left eye for a few days. He did not have any relevant past medical history or smoking history. His ECOG performance status (PS) was 1 due to visual disturbance. Funduscopy and fluorescence angiography (FA) showed retinal detachment and choroidal tumor. A 5-cm diameter tumor

was found in the right lower lung on X-ray. He was referred to our hospital with the suspicion of lung cancer with choroidal metastasis. A CT scan showed a 36×23 mm tumor in the right lower lung (S⁹ region); CT and MRI of orbit with contrast showed it was intact. ¹⁸F-FDG PET/CT demonstrated FDG accumulation in the right lung tumor, entire bone marrow, mesentery, and the dorsal side of the left eye (Figure 1A–1C). His complete blood count (CBC) and blood chemistry revealed leukocytosis (WBC 11 630 /uL) and high alkaline phosphatase (ALP 2215 U/L), suggesting bone marrow metastasis. Serum levels of carcinoembryonic antigen (CEA) and sialyl Lewis-x antigen (SLX) were 282.7 ng/mL and 176.2 U/mL, respectively.

A transbronchial lung biopsy (TBLB) revealed the lung tumor as adenocarcinoma; the staging was cT2N0M1b (OSS, OTH) stage IV. On the ophthalmology examination, his visual acuity was 1.2 OD and 0.4 OS. Funduscopic examination showed an elevated lesion with a 6-disc diameter in the left superior of the optic nerve. Spectral-domain optical coherence tomography (OCT) showed exudative fluid, which caused retinal detachment under the retina. FA showed granular hyperfluorescence with the leakage consistent with a tumor (Figure 1D–1G).

For palliative therapy for bone metastasis, radiotherapy targeting the cervical spine and pelvis was carried out, with a total dose of 37.5 Gy, given as 2.5 Gy/fraction per day. Systemic chemotherapy; carboplatin (AUC 6) + pemetrexed (500 mg/m²) + bevacizumab (15 mg/kg) was performed. The choroidal metastasis and exudative retinal detachment improved on fundus examination. He received additional local therapy. Intravitreal injection of bevacizumab 1.25 mg was also performed 20 days after the systemic therapy, with his informed consent. The choroidal metastasis was no longer visible and exudative retinal detachment improved on fundus examination after 27 days of systemic chemotherapy (Figure 1H, 1I).

After 1 cycle of the systemic chemotherapy and local therapy, he developed stomatitis and his PS decreased gradually. Thus, no further chemotherapy was given. He died of lung cancer 60 days after the systemic chemotherapy was begun. His autopsy showed that the primary site was well-differentiated lung adenocarcinoma at the right lower lung, with a size of 40×30×25 mm. We also observed multiple pulmonary and bone metastasis, mild pancreatitis, and severe pseudomembranous enterocolitis. His left eye was intact macroscopically and microscopically, suggesting the complete cure of the choroidal metastasis (Figure 2A–2G).

Discussion

Intraocular metastasis is commonly located in the posterior uvea because of its rich blood supply. Prevalence figures

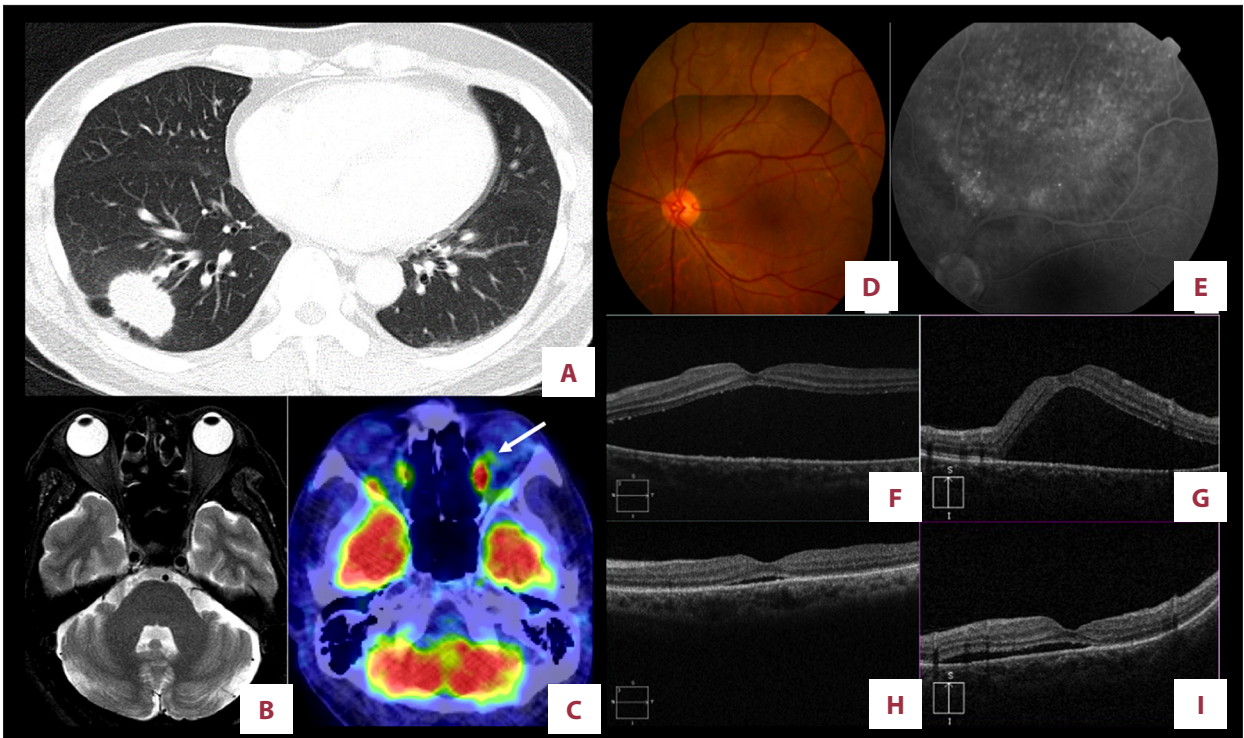


Figure 1. Chest CT, PET, and ophthalmic examination. (A) CT showed a tumor in the right lower lung. (B) Although the eyes were intact in MRI, (C) FDR accumulated at the dorsal of the left eye (arrow). (D) Fundusoscopic findings; an elevated lesion is present in the left superior fundus of the optic nerve, 6 discs in size. (E) Fluorescein angiography indicated multiple hyperfluorescent spots. (F, G) OCT showed retinal detachment by the subretinal fluid. (H, I) The retinal detachment improved after the chemotherapy.

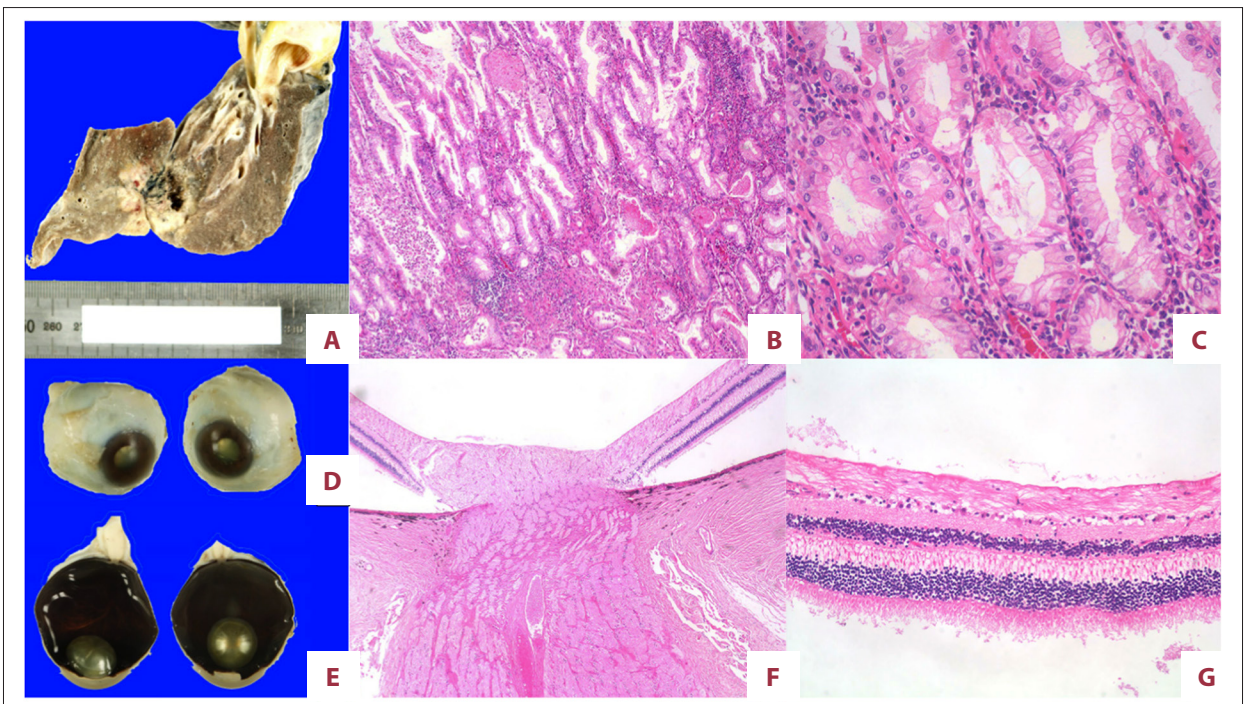


Figure 2. Pathological analysis. (A) Lung cancer in the right lower lung. (B, C) Histopathologic examination demonstrated adenocarcinoma of the lung. (D, E) Macroscopic findings of left eye intact. (F) Choroid membrane was also intact. (G, H) Microscopic findings showed no tumor cells or retinal detachment.

calculated from screening studies in patients with metastatic cancer suggest that choroidal metastasis is the most frequent intra-ocular tumor [12]. The most common intraocular tumor is choroidal metastasis from lung cancer in men and breast cancer in women [1]. Prognosis of the choroidal metastasis depends on its primary site. The mean survival time (MST) of patients with choroidal tumor from lung cancer is 7.9 ± 1.8 months and for patients with clinical stage IV non-small cell lung cancer mean survival time is 6 months. In addition, the MST of choroidal metastasis from breast cancer is 21.8 ± 4.2 months and that of stage IV breast cancer is 18–24 months [5,13,14]. Treatment options include: 1) observation if the patient is pre-terminal or the metastases appears regressed; 2) chemotherapy, immunotherapy, hormone therapy, or whole-eye radiotherapy if the metastases are multifocal, bilateral, or associated with extensive subretinal fluid; 3) plaque radiotherapy for solitary metastasis; and 4) enucleation is considered in very limited cases such as choroidal metastasis that is progressive and causes refractory pain [15,16].

Bevacizumab, a recombinant anti-VEGF monoclonal antibody, inhibits new blood vessel formation and growth. It is used alone or in combination with other anticancer drugs in patients with advanced colon, lung, breast, renal, and ovarian cancer [17–19]. In our case, the patient was treated with the regimen of carboplatin, pemetrexed, and bevacizumab, which is often used as an initial treatment of advanced nonsquamous NSCLC [20].

Intravitreal bevacizumab is a newer modality being tried for local control of choroidal metastases [21]. Currently, its use in this indication is off-label. Intravitreal bevacizumab has been used to treat choroidal metastases from breast cancer, colorectal carcinoma, and lung cancer [6]. Successful metastasis is dependent on angiogenesis at the metastatic site. Thus, inhibition of tumor-induced angiogenesis is very suitable for metastasis treatment via blood circulation [7,8]. Intravitreal bevacizumab for choroidal metastases from lung cancer has recently been reported, and 11 cases of choroidal metastasis from lung cancer have been reported. In 2 cases of SCLC, intravitreal bevacizumab was not effective, but it improved choroidal metastasis in 7 of 9 NSCLC cases. Intravitreal bevacizumab is a promising

alternative to ocular radiation, especially for treatment of non-small non-squamous lung cancer [1,10,11].

In our case, systemic chemotherapy was performed before the intravitreal bevacizumab and improved choroidal metastasis. The left choroidal metastasis at the time of local therapy had disappeared by the time of death, but the primary tumor size showed slight progression at autopsy. The additional effect of local treatment is actually unclear; however, it is considered that local therapy contributed to the further effect.

Finally, systemic chemotherapy and additional intravitreal bevacizumab definitely cured the choroidal metastases, which was confirmed by autopsy. Although several case reports have been published on intravitreal bevacizumab as a therapy for choroidal metastasis from lung cancer, this is the first report to assess choroidal metastasis treated with intravitreal bevacizumab with results confirmed by autopsy.

Although the benefits of intravitreal bevacizumab may need to be evaluated in trials, this may not be feasible because of the rarity of the choroidal metastasis.

Conclusions

In conclusion, we report a case of exudative retinal detachment secondary to metastatic choroidal tumor from lung adenocarcinoma, treated with chemotherapy and intravitreal injection of bevacizumab. Our patient eventually died of lung cancer but his visual symptom had improved and the choroidal metastasis was in complete remission.

Acknowledgement

We thanked to Dr. Hara for research advice. We are grateful to Drs Suganuma, Mashimo, and Mitake for writing advice.

Disclosure statement

The authors have no conflicts of interest.

References:

1. Maturu VN, Singh N, Bensal P et al: Combination of intravitreal bevacizumab and systemic therapy for choroidal metastases from lung cancer: report of two cases and a systemic review of literature. *Med Oncol*, 2014; 31: 901
2. Inagaki E, Hajime S, Atsuro U et al: Effect of intravitreal injection of bevacizumab for exudative retinal detachment secondary to metastatic choroidal tumor: case report. *Atarasi Ganka (Journal of the Eye)*, 2011; 28: 587–92
3. Katsutoshi A, Akina K, Masanori M et al: Factors affecting visual outcome in cases of lung cancer with choroidal metastasis initially presenting with ocular symptoms. *JJLC*, 2011; 51: 94–98
4. Jardel P, Sauerwein W, Olivier T et al: Management of choroidal metastases. *Cancer Treat Rev*, 2014; 40: 1119–28
5. Kreusel KN, Bechrakis N, Wiegel T et al: Clinical characteristics of choroidal metastasis. *Ophthalmologe*, 2003; 100: 618–22
6. Klaassen I, Van Noorden CJ, Schlingermann RO: Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. *Prog Retin Eye Res*, 2013; 34: 19–48
7. Lauro S, Onesti CE, Righini R et al: The use of bevacizumab in non-small cell lung cancer: an update. *Anticancer Res*, 2014; 34: 1537–45
8. Ferrara N: VEGF and the quest for tumour angiogenesis factors. *Nat Rev Cancer*, 2002; 2: 795–803

9. Tari SR, Youssif M, Samson CM et al: Polychromatic angiograph for the assessment of VEGF-induced BRB dysfunction in the rabbit retina. *Invest Ophthalmol Vis Sci*, 2013; 54: 5550–58
10. Fenicia V, Abdolrahimzadeh S, Mannino G et al: Intravitreal bevacizumab in the successful management of choroidal metastases secondary to lung and breast cancer unresponsive to systemic therapy: a case series. *Eye (Lond)*, 2014; 28: 888–91
11. Maudgil A, Sears KS, Rundle DA et al: Failure of intravitreal bevacizumab in the treatment of choroidal metastasis. *Eye (Lond)*, 2015; 29(5): 707–11
12. Kreusel KM, Bechrakis NE, Wiegel T et al: Incidence and clinical characteristics of symptomatic choroidal metastasis from lung cancer. *Acta Ophthalmol*, 2008; 86: 515–19
13. Goldstraw P, Crowley J, Chansky K et al: The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM staging groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumors. *J Thorac Oncol*, 2007; 2: 706–14
14. Babiera G, Khan SA: Treatment of stage IV breast cancer with intact primary tumor: a case for resection? *Curr Breast Cancer Rep*, 2012; 4: 153–60
15. Ye X, Kaliki S, Shields CL: Rapid regression of choroidal metastasis from lung cancer using erlotinib (Tarceva). *Oman J Ophthalmol*, 2014; 7: 75–77
16. Lumi K, Yuriko B, Yusuke Y et al: A case of choroidal metastasis from small-cell lung carcinoma diagnosed through ocular symptoms. *Atarashii Ganka (Journal of the Eye)*, 2009; 26: 1687–91
17. Yasui H, Sato K, Takeyama Y et al: Carcinoma of unknown primary site treated with carboplatin + paclitaxel + bevacizumab + erlotinib and its maintenance chemotherapy. *Case Rep Oncol*, 2014; 7: 583–90
18. Sato K, Takeyama Y, Yoshihara M et al: CBDCA + Pemetrexed + Bevacizumab and Its Maintenance Chemotherapy in a Case of Solitary Breast Metastasis from a Lung Adenocarcinoma Resistant to Gefitinib. *Case Rep Oncol*, 2012; 5: 546–53
19. Yasui H, Sato K, Takeyama Y et al: Granulocyte colony-stimulating factor-producing carcinoma of unknown primary site. *Case Rep Oncol*, 2014; 7: 780–88
20. Patel JD, Socinski MA, Garon EB et al: PointBreak: a randomized phase III Study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*, 2013; 31: 4349–57
21. Amsellem L, Cervera E, Diaz-Llopis M et al: Intravitreal bevacizumab (Avastin) for choroidal metastasis secondary to breast carcinoma: short-term follow-up. *Eye (Lond)*, 2007; 21: 566–67