

Treatment of choroid metastasis from lung adenocarcinoma with bevacizumab-containing chemotherapy: A case report

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Abstract. The occurrence of ocular metastasis from lung cancer is uncommon. The present study reports the case of a 69-year-old female patient with lung adenocarcinoma who was found to have a metastatic lesion in the left choroid at the time of presentation. As the patient was found to have a mutation in the epidermal growth factor receptor, treatment with gefitinib was administered; however, the response was evaluated as a progressive disease. Thereafter, the patient received chemotherapy with carboplatin, pemetrexed and bevacizumab. Radiological imaging revealed shrinkage of the primary lesion and choroidal metastasis, and the visual power of the left eye was also shown to improve. Therefore, the present case report demonstrated the efficacy and safety of systemic bevacizumab therapy in combination with a platinum doublet for the treatment of choroid metastasis, with morphological and functional improvements observed with regard to the choroidal metastatic tumor.

Introduction

Although rare, metastatic choroid tumors are the most common type of intraocular malignancy. The frequency of intraocular metastasis in all patients dying of cancer was reported to be approximately 12% (1). Lung and breast cancers are two of the predominant tumors to metastasize to the eye (2,3). Among the ocular metastases, the choroid is the most commonly affected site (2). The prognosis for patients with ocular metastases remains inadequate. For these patients life expectancy is reported to be between 2-48 months (median 6-9 months)(4,5). Radiotherapy remains the main type of therapy and allows the majority of patients to maintain a good vision for as long as they are alive (1). Recently, the development of molecular

targeted therapies, such as humanized antivascular endothelial growth factor, bevacizumab and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors, has improved the survival rate of patients with advanced non-small cell lung cancer (NSCLC), without substantially increasing the toxicity (6). The present study reports the case of a patient with NSCLC and choroid metastasis who was successfully treated with bevacizumab-containing chemotherapy, following treatment failure with gefitinib.

Case report

A 69-year-old female that had been newly diagnosed with a metastatic adenocarcinoma of the lung presented with a one-month history of blurred vision in the left eye. The best corrected visual activity (BCVA) in the left eye was 20/200. A chest radiograph and computed tomography (CT) scan revealed a pulmonary mass in the left upper lobe with ipsilateral mediastinal lymph node swelling (Fig. 1). In addition, pleural fluid was observed in the left lung, while metastases were identified in both lungs, the paraaortic lymph nodes of the abdomen and the right adrenal gland. A brain CT scan revealed a choroidal tumor in the left eye that measured 10.4x6.4x2.6 mm in size (Fig. 2). Pathological diagnosis of the lung mass, which was obtained via a transbronchial biopsy, revealed an adenocarcinoma. Using the specimen obtained from the primary lesion by bronchoscopy, an EGFR mutation was evaluated using a PCR clamp method. The PCR clamp method preferentially amplifies mutation sequences and detects mutations. The method requires a peptide nucleic acid (PNA) clamp primer and locked nucleic acid (LNA) probe. PNA clamp primers bind to the wild type sequence and suppress their amplification, whereas LNA probes are designed to specifically detect mutant sequences and enhance their amplification in the presence of wild type sequences, since PNA clamp primers competitively inhibit the ability of mutant LNA probes to bind to wild type sequences. To detect mutations of exons 18, 19, 20 and 21, a total of 12 probes were used. The PCR clamp method was performed by Mitsubishi Kagaku Bio-Clinical Laboratories, Inc. (Tokyo, Japan). As the patient had a mutation in the EGFR gene (exon 21 L858R), treatment with gefitinib was initiated. However, the BCVA of the left eye continued to deteriorate to 'mortus manus' (finger movement) and the

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pleural fluid in the left lung increased. Therefore, the response was evaluated as a progressive disease. Subsequently, the patient received chemotherapy with carboplatin (AUC 5, day 1, q28), pemetrexed (500 mg/m², day 1, q28) and bevacizumab (15 mg/mg, day 1, q28). A brain CT scan performed after two cycles of the chemotherapy revealed the disappearance of the choroidal lesion (Fig. 3). In addition, an improvement in vision of up to 20/200 was observed. Subsequently, the patient completed four cycles of the chemotherapy and attained a partial response. The patient received additional maintenance chemotherapy with pemetrexed (500 mg/m², day 1, q28) and bevacizumab (15 mg/mg, day 1, q28). The patient survived for 16 months after the diagnosis of lung adenocarcinoma, with no evidence of deterioration of vision. Written informed patient consent was obtained from the patient's family.

Discussion

Breast and lung cancers are the most common primary tumors that metastasize to the eye and orbit (2,3,7), and the most commonly affected part of the eye is the vascular uveal tract (7). Within the uvea, the choroid is the most frequently affected site of metastasis (2). As observed in the patient in the present study, the majority of patients have metastatic lesions elsewhere at the time of diagnosis of ocular involvement (8). As a result of such metastasis, the treatment for ocular metastasis may be palliative and the aims for treatment are to maximize the quality of life and restore or preserve vision.

Certain case reports have demonstrated that chemotherapy is efficacious for choroid metastases from NSCLC (9,10). To the best of our knowledge, there have been seven case reports that precisely describe the outcome of bevacizumab-containing chemotherapy for the treatment of choroid metastasis (11-16). The characteristics of these studies are outlined in Table I. In four cases, the patient was diagnosed with adenocarcinoma. However, no information was provided with regard to EGFR gene mutations in any of the patients. In all the cases, improvement was observed in the choroid metastasis, as well as functional improvement in visual power. In four cases, including the present study, systemic bevacizumab-containing chemotherapy was applied (one patient received cisplatin-based therapy and three patients received carboplatin-based chemotherapy) (11,14,16). Kim *et al* reported successful treatment with oral erlotinib and intravitreal therapy with bevacizumab (12). In the present case, gefitinib was not effective for the intrathoracic and intra-ocular lesions, despite the detection of a mutation in the EGFR gene. Lai *et al* reported the successful treatment of a case with intravitreal bevacizumab therapy, without administration of systemic chemotherapy (15). Visual power in this patient was shown to improve; however, the patient succumbed four months after the diagnosis (15). By contrast, D'Antonio *et al* presented a case who was successfully treated with systemic bevacizumab-containing chemotherapy and survived for over 20 months (14). In the present study, the patient survived for 16 months following the diagnosis of lung cancer. However, the prognosis of choroid metastasis from lung cancer is very poor, with a mean life expectancy of 1.9 months (4). This short survival time is not due to the choroid metastasis itself, but the condition of disease dissemination with the involvement

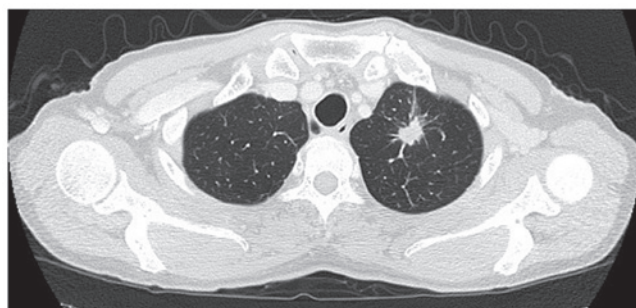


Figure 1. Chest computed tomography scan at the initial presentation revealed a mass in the upper lobe of the left lung with pleural fluid.



Figure 2. Brain computed tomography scan at the initial presentation revealed a metastatic tumor (size, 10.4x6.4x2.6 mm) in the choroid of the left eye (arrow).

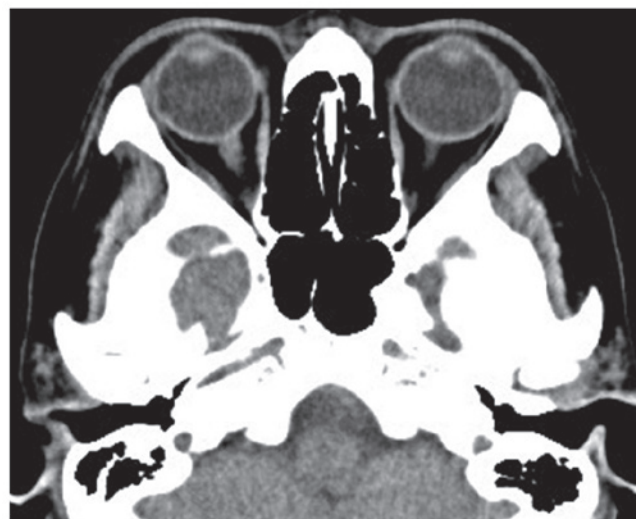


Figure 3. Brain computed tomography scan following two cycles of bevacizumab-containing chemotherapy revealed the disappearance of the choroid tumor in the left eye.

of other vital organs. The four patients treated with bevacizumab and the current patient had metastatic sites other than in the choroid. Singh *et al* reported two cases treated

Table I. Patients treated with bevacizumab.

Age gender	Symptom	Duration of symptoms	Pretreatment visual power	Affected eye	Lung cancer	EGFR mutation	Other metastatic sites	Size of choroid metastasis (mm)	Intravitreal BEV	Systemic chemotherapy	Improvement of choroid metastasis	Visual power after therapy	Systemic effect	Toxicity	Survival (months)	First author, year
42 F	Blurred vision	1 week	nd	Right	LA	nd	Lung, cervical LN	12x12x6.3	No	CBDCA+GEM +BEV	Complete resolution	Improved	PR	None	Alive	George, 2009
57 F	Decreased vision	3 month	BCVA 20/200	Left	AD	nd	Multiple metastases	8.37x7.56x2.48, 7.52x6.21x2.94	Yes	Erlotinib	Completely disappeared	Improved to 20/40	nd	None	nd	Kim, 2009
53 M	Decreased vision	1 month	20/50	Left	AD	nd	Lungs	nd	Yes	TS-1	20/100	Improved to 20/25	nd	None	5	Inagaki, 2011
34 F	Vision loss, diplopia	nd	nd	Left	AD	nd	nd	Big (size, nd)	Yes	CDDP+GEM BEV	Dimensional reduction	Complete recovery	SD	None	20 (alive)	D'Antonio, 2012
73 M	Decreased vision	nd	BCVA 20/200	Left	AD	nd	Stage IV (nd)	nd	Yes	Not done	Regression of tumor size	Improved to 20/60	nd	None	4	Lai, 2012
42 F	Diminished vision	1.5 month	2/60	Left	NSCLC	nd	Liver	14.8x13.0x4.1	Yes	CDDP+PAC	Complete resolution	Improved to 6/120	nd	None	9	Singh, 2012
53 M	Loss of vision	3 month	Mortus Manus	Right	NSCLC	nd	Liver, bone, adrenal gland	15.0x14.5x6.3	Yes	CBDCA+DOC +BEV	Decreased	Improved to 6/24	nd	None	16	Singh, 2012
69 F	Blurred vision	1 month	Mortus Manus	Left	AD	Exon 21, L858R	Lung, abdominal LN, adrenal	10.4x6.4x2.6	No	CBDCA+PEM +BEV	Completely disappeared	Improved to 20/100	PR	None	16	Present case

Mortus manus means finger movement in Latin. F, female; M, male; BCVA, best corrected visual activity; LA, AD, adenocarcinoma; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; nd, LN, lymph node; BEV, bevacizumab; CBDCA, carboplatin; GEM, gemcitabine; CDDP, cisplatin; PAC, cyclophosphamide; DOC, docetaxel; PEM, pemetrexed; PR, partial response; SD, stable disease; LA, large cell lung cancer; nd, not described.

with bevacizumab-containing chemotherapy. In one of these patients, first line chemotherapy without bevacizumab was not effective for the choroid metastasis; however, second line chemotherapy with bevacizumab-containing chemotherapy achieved resolution of the choroid metastasis and visual improvement (16). Notably, the patient in the present study received bevacizumab-containing chemotherapy as the second line treatment and also achieved resolution of the choroid metastasis and visual improvement. These results suggested that systemic chemotherapy with bevacizumab may have an significant role in improving visual power as well as survival of the patients.

Intravitreal bevacizumab administration has been used to treat choroid metastases from organs other than the lungs (17,18). In these two studies, antiangiogenic and antipermeability effects of bevacizumab were observed on the new tumor vessels by fluorescein angiography. These observations demonstrate the obligate and vital dependence of choroidal tumors on angiogenesis, which forms the rationale for the use of intravitreal bevacizumab administration, regardless of the fact that a platinum doublet in combination with bevacizumab is one of the chemotherapy options for the treatment of lung cancer patients with choroid metastasis. Two of the patients who were treated with systemic bevacizumab-containing chemotherapy received intravitreal administration of bevacizumab (14,16) (Table I).

In conclusion, the present case report demonstrated the efficacy and safety of systemic bevacizumab therapy in combination with a platinum doublet for the treatment of choroid metastasis, with resulting morphological and functional improvements in the choroidal metastatic tumor. Therefore, systemic administration of bevacizumab with intravitreal injections may be selected as a therapeutic approach due to the greater potential to produce effective chemotherapeutic concentrations around the metastasis site via the rich choroidal blood supply, which is within the systemic circulation and not protected by the blood-retina barrier.

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