Clinical Presentation, Diagnosis and Treatment of Choroidal Metastasis from Primary Lung Cancer

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Abstract

Metastasis to the choroid is not uncommon. The most common primary tumor to metastasize to the choroid is lung in men and breast in women. It may present with blurry vision, decreased vision with photopsiae, or pain. There have been changes over years in the diagnosis of the local ocular tumor, primary disease and other distant metastases. Advanced tools such optical coherence tomography, fluorescein angiography along with indocyanine green angiography and position emission tomography along with computerized tomography are helpful in both differential diagnosis and pre & post treatment changes of the local and systemic lesions. The newer trends in the treatment such as intravitreal chemotherapy along with systemic therapy, plaque radiotherapy, proton beam therapy and photodynamic therapy has lead to less ocular complications with better choroidal metastasis regression, improvement in visual acuity thereby providing better quality of life in patients with short-term survival. The recently updated lung cancer screening guidelines by “the US Preventive Services Task force” helps in shared decision making to screen these patients which leads to the early diagnosis and treatment of the primary tumors thereby reducing the mortality related to the lung cancers.

Keywords: Choroid metastasis; External beam radiotherapy; Non-small cell lung cancer; Plaque radiotherapy; Photodynamic therapy

Introduction

Uveal metastasis is the most common intraocular tumor [1,2]. Choroid is the most common site of metastasis (>80%) in eye due to its rich vascular plexus. In men, the common primary tumor metastasizing to choroid is the lung (~20%). Of which, most common lung tumor is a non-small cell lung cancer (85%) (NSCLC) than small cell lung cancer (SCLC) [2-4]. In women, the most common primary tumor metastasizing to the choroid is breast. Others primary tumors metastasizing to the choroid are liver, unknown primary, pancreas, kidney, gastrointestinal tract (GITT), and rarely prostate & testis (men) and uterus & ovary (women). The incidence of choroidal metastases from lung varies from 2-7% [1,2,5-8].

Clinical features

Choroidal metastasis (CM) can be the first manifestation of a disseminated lung cancer [1,2,6]. It is commonly found among men who are smokers or ex-smokers at approximate age of 55 years [2,6,9]. At initial presentation, patients may be asymptomatic or may present with blurry vision, diminution of vision, occasional floaters, flashes of light, decrease in visual fields and redness. Sometimes, they solely present with painful blind eye due to neovascular glaucoma. Lung metastasis to the choroid is usually unilateral, unifocal and oligometastasis but they can also be bilateral and multifocal [3,6]. The lesions are usually non-pigmented (yellow or orange), located most commonly posterior to the equator (>80% are in posterior pole region). There may be overlying retinal pigment epithelial (RPE) changes showing some black pigment occasionally. Associated clinical features include serous retinal detachment (RD), vitreous hemorrhage, retinal hemorrhages, choroidal neovascularisation and retinal edema with or without involving the fovea depending on the location of the tumor, subretinal lipid exudates and rarely rubeosis iridies with neovascular glaucoma.

Diagnosis

Few patients of CM may present initially without a diagnosis of prior lung cancer that require thorough work-up to detect the primary tumor along with ophthalmic evaluation [2,6]. All patients need complete ocular examination including best corrected visual acuity (VA), slit-lamp biomicroscopy, binocular indirect ophthalmoscopy, fundus photography, fundus autofluorescence...
(AF), fundus fluorescein angiography (FFA), indocyanine green angiography (ICG-A), optical coherence tomography (OCT), A and B scan ultrasonography (USG), computerized tomography (CT) of the chest, magnetic resonance image (MRI) of the abdomen and blood work for the liver function tests. Staging work – up for the primary lung cancer additionally will be performed by the medical oncologists.

Color fundus photographs reveal the above described clinical findings and are helpful to explain the changes of the tumors pre and post treatment.

Fundus autofluorescence (AF) is a non-invasive method used to detect changes in the RPE. Hyperautofluorescence on AF is indicative of lipofuscin deposits in RPE cells, and hypoautofluorescence is indicative of loss or damage to the RPE, whereas continuous pattern on AF is indicative of normal function of RPE cells overlying the tumor. AF is the best test to show the overlying tumor features and its margins. In CM, hyperautofluorescence is seen at the areas of RPE thickening, subretinal fluid (SRF) and advanced tumor edges and hypoautofluorescence is seen at the areas of RPE loss. AF also shows changes with tumor growth and is used in the follow-up after treatment [10,11].

Spectral-Domain Optical coherence tomography features includes thickened choroid at the level of tumor with presence of SRF, retinal folds, retinal thickening due to edema and serous RD [10,12]. Recently the newer OCT technique, Heidelberg-Spectralis OCT with enhanced depth imaging (EDI) in patients with CM revealed normal inner retinal layers, lumpy bumpy anterior tumor surface with outer retinal layer irregularities, overlying irregularity of the RPE with its thickening & undulations, subretinal lipofuscin, SRF, intraretinal edema, obliteration or compression of choriocapillaries, and posterior shadowing [13]. After treatment of choroidal metastasis, thinning of the retina, irregular or loss of RPE, chorioretinal atrophy and resolution of the SRF/edema is seen on OCT [12,13].

Fundus fluorescein angiography (FFA) features of choroidal metastasis are difficult to distinguish from choroidal melanoma and hemangioma. In choroidal metastasis, there may be areas of hyperfluorescence in the early phases followed by progressive fluorescence in mid phase and diffuse fluorescence in late phases. Occasionally there may be only early hyperfluorescence with decrease in fluorescence at late phase [10,14]. FFA also shows features of persistent pinpoint leakages at the border of the lesion secondary to retinal capillary dilation, a feature that distinguishes a choroidal metastatic lesion from a melanoma [15].

Indocyanine green angiography (ICG-A) is an advanced diagnostic clinical tool currently available to evaluate the non-pigmented choroidal lesions. It is especially helpful to identify the tumor vascular pattern thereby differentiating amelanotic choroidal melanoma and metastasis from hemangioma. In patients with associated serous RD around the lesion, ICG-A shows clear visualization of the tumor through retina unlike FFA. It may reveal areas of hypofluorescence in early phases followed by hyperfluorescence in very late phase [16,17]. Compared with FFA, it shows smooth, regular hypofluorescent margins showing the exact size of the metastatic tumor. There is blockage of background staining in all cases of metastasis and melanomas. Unlike in choroidal hemangioma which shows double circulation-retina and tumor), metastasis does not show marked tumor vessels whereas melanoma shows some intrinsic tumor vessels.

After treatment, ICG-A shows no dye accumulation suggesting the inactivity of the lesion [16-18].

Ultrasoundography (USG) is a helpful diagnostic tool especially in patients with amelanotic choroidal melanoma which clinically resembles the choroidal metastasis. On USG, there may be some overlap of features for choroidal metastasis and melanoma depending on the tumor vascularity, solidity, and choroidal excavation [19]. With CM, USG A-scan shows a high spike at the level of the lesion revealing high internal reflectivity (unlike choroidal melanoma which has low to medium intensity spikes). USG B-scan in CM demonstrates a plateau or dome shaped tumors and ± RD (choroidal melanoma can be plateau, dome or mushroom shaped lesions ± RD). Most of the studies demonstrated mean tumor thickness of > 3 mm on B-scan USG [2,7,19,20].

Fine needle aspiration biopsy (FNAB) is a highly accurate diagnostic test to confirm the presence of both anterior and posterior segment tumors of the eye. It can be done through transvitreal route with a 27 G needle and has an accuracy of 90-98% in lesions of > 2 mm in thickness [21,22]. FNAB has a high yield of up to 99% with relatively few complications. Histopathologically, most common cell type in CM is adenocarcinoma followed by squamous cell carcinoma & small cell carcinoma, and rarely leiomyosarcoma [1,3,6,7,9,23].

Positron emission tomography (PET) scan, a newer imaging modality used to detect lesions not visible by other imaging techniques or where magnetic resonance imaging (MRI) is contraindicated. Combined PET/CT is a useful tool to detect not only the lesions in choroid, primary tumors and other distant metastases but also helpful to assess the tumor response after treatment [24].

Regular systemic follow-up to treat the primary lung tumor is done in all patients with CM. Chest x-ray may not show lung lesions in many patients at first visit. Computerized tomography (CT) scan is helpful in detecting the local lung tumors (most common location is left upper lobe). MRI scan is useful in diagnosis and follow-up of metastatic lesions from lung cancer.

**Treatment**

The goal of treatment is to preserve the globe, restore or stabilize the vision and improve quality of life. Treatment regimen varies depending on the size, extent, number of tumors, location & laterality of tumors, visual acuity status of the affected eye, stage of systemic disease, presence of other distant metastasis, age and overall general health of the patient [25,26]. Treatment options are observation, chemotherapy (intravitreal anti-vascular endothelial growth factors (anti-VEGF), systemic), radiotherapy (external beam (EBRT), plaque brachytherapy and proton beam therapy (PBT)), laser therapy (transscleral thermotherapy (TTT), photodynamic therapy (PDT)), immunotherapy, hormone therapy and enucleation [20,25-29]. Spontaneous regression of choroidal metastasis is rare. Observation can be done in patients of advanced disease with poor systemic status or those with small, unilateral, asymptomatic tumors. Associated systemic chemotherapy may regress the unilateral, solitary, small tumors in patients with NSCLC than those with SCLC [9]. Systemic chemotherapy agents alone such as cisplatin, gefitinib or erlotinib, alectinib and bevacizumab may partially regress the CM [9,23,26].

Intravitreal bevacizumab was tried recently along with systemic chemotherapy in CM from NSCLC. It was used at doses of either 1.25 mg or 2.5 mg varying from 2 to 14 injections with duration...
between them of 2 weeks to 2 months. Intravitreal anti-VEGF therapy showed favorably good local tumor control with no major ocular complications. This treatment modality can be promising to be a safe alternative to RT in the initial stages of NSCLC when combined with systemic chemotherapy [27].

Before plaque radiotherapy, external beam radiotherapy is performed as a standard method of treatment. It is a safe and effective palliative treatment option in the treatment of CM. It is used for large, multifocal, and bilateral choroidal tumors. EBRT is performed in combination with systemic chemotherapy depending on the stage of the lung cancer. The radiation dose usually applied is 30 Gy in 10 fractions or 40 Gy in 20 fractions with lens sparing unilateral field for unilateral CM and bilateral fields for bilateral CM [25,28,29]. EBRT quickly reduces the ocular symptoms, controls the local tumor, and achieves good functional outcomes. Tumor response was good with EBRT and has a success rate of up to 93% [30]. Few studies reported recurrence of the metastasis or developed metastasis in the fellow eye with EBRT [29]. The early side effects of EBRT are skin erythema, conjunctivitis, keratitis and late side effects are cataract, glaucoma, vitreous hemorrhage, radiation papillopathy, maculopathy & retinopathy and choriorretinal atrophy [8,25,28,29,31].

Plaque brachytherapy is an effective alternative treatment when other methods of treatment failed. It is used for selective solitary metastasis to the choroid and provides rapid and effective tumor control. After the other distant metastatic sites have been ruled out or in patients with stable distant metastasis, this very focal treatment modality is usually used. Various ocular oncologists used different materials such as Iodine (1-125) or Ruthenium (Ru-106) or Palladium-103 for treating the CM. It is delivered to the eye as in-patient technique over a period of approximately 3 days unlike EBRT which requires 3-4 weeks. The radiation dose ranges approximately from 60-70 Gy to the apex of the tumor. This precise focal radioactive plaque therapy for CM is very effective with 94% success rate in tumor regression. Like EBRT it also preserves the globe, restores/stabilizes the VA. It avoids radiation complications to the neighboring structures in the eye and has less radiation toxicities unlike EBRT [26,30,32].

Proton beam therapy (PBT) consists of treating the CM with 2 fractions of 14 cobalt gray equivalents (CGEs), each using a non-operative “light-field” technique (unlike EBRT, where 10-20 fractions over 3–4 weeks is needed depending on the radiation dose). There is almost complete tumor regression with no signs of recurrence with PBT. Tumor response with PBT was good with a success rate of 98% [30]. Like other RT techniques; this therapy also allows retention of globe and stabilizes visual acuity. PBT toxicities include macarosis, ocular surface syndrome, keratitis, cataract, neovascular glaucoma, radiation papillopathy, maculopathy & retinopathy and choriorretinal atrophy [20].

Transpupillary thermotherapy (TTT) combined with plaque radiotherapy enhances tumor shrinkage, inhibits tumor growth, prevents progression of tumor growth in moderate sized choroidal metastases. TTT alone can be performed for small single tumors located in the posterior pole. It fastens the flattening of the tumor when combined with plaque RT. It is performed using 810 nm infrared diode laser with spot sizes of 0.5–3 mm in 1–3 sessions every 3 months after plaque RT or alone. TTT works by causing tumor necrosis. TTT improves the visual acuity fast in patients with posterior pole lesions with minimal SRF, but precautions need to be taken in case of tumors nearer to the optic nerve head and foveola. The local side effects of TTT are retinal traction, retinal vascular occlusions, and damage to the fovea if the lesion is close to the fovea and optic disc edema in lesions located near to the optic nerve head [33,34].

Photodynamic therapy (PDT) can be an alternative tertiary treatment modality in patients with CM that is resistant to both chemotherapy and radiotherapy. PDT is applied with a 4 minute prior intravenous infusion of verteporfin (dose of 6 mg/m2 body surface area) followed in 5 minutes by a 689 nm diode laser at an intensity of 600 mW/cm2 for 83 seconds. It may require 1-3 sessions of PDT to get good treatment response. PDT works by destroying tumor cells by producing high oxygen radicals and activating the immune response against tumor cells and abolishing the intrinsic tumor vessels, thereby leading to CM regression. SRF resolution leads to fast improvement of VA. This procedure requires less effort and time, has few complications and is a better alternative method in patients with short life span who has compromised systemic status [35–37].

Enucleation is performed as a last option when all other above treatment methods failed to regress the CM. Painful blind eye with neovascular glaucoma or extracapsular/orbital extension of CM are indications for enucleation surgery. It provides better quality of life in advanced primary disease [6,38,39].

**Future lung cancer screening guidelines**

Patients with NSCLC have increased rates of survival due to improvements in the curative treatments and advanced screening methods [40]. The US Preventive Services Task Force (USPSTF) recommendations for screening lung cancer are annual screening with low-dose CT for asymptomatic adults aged 55 to 80 years with a 30 pack-year smoking history, who currently smoke or have quit within the past 15 years [41]. Improved screening techniques have led to better quality of life in high-risk patients.

**Conclusion**

Overall survival of patients with CM in lung cancer is limited to less than 6 months to 1 year [6,42]. Multidisciplinary approach is required in symptomatic choroidal metastases patients with associated primary tumors, which improves the quality of life of patients both ocular and systemic. Though systemic prognosis is poor, local treatment helps in globe salvage and improves the visual acuity. Combined treatment modalities provide better control of local and systemic tumor. Newer and focal treatment modalities have reduced the RT related complications. Chest x-ray may not show lung lesions at initial visit in many patients. CT scan of the thorax is helpful in detecting the local lung tumors. PET scan finds out both local lung lesions and distant metastases and currently is very much used tool by many oncologists in the follow-ups after treatment. Systemic screening helps in early detection of the primary tumors and distant metastasis thereby improving the quality of life the patients. However, due to short life of the patients with CM, systemic screening of at-risk patients has limited benefit.

**References**


