· Review ·

Current research progress of choroidal metastasis

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脉络膜转移癌的最新研究进展

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摘要

脉络膜转移癌是眼部最常见的恶性肿瘤之一。其症状表现为眼部疼痛、视力下降等,从而降低了患者的生活质量。早期发现和早期治疗可改善患者视力,延长患者寿命,意义重大。因此,脉络膜转移癌的治疗方式迅速发展。靶向药物和基因治疗的玻璃体腔注射是研究的热点。本文主要叙述了目前脉络膜转移癌的病因、发展、诊断和治疗方法。

关键词:脉络膜转移癌;症状;治疗

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Abstract

• Choroidal metastasis is one of the most common malignant tumors inside the eyes. It causes pain, hypopsia and some other related symptoms. It reduces the quality of the patients' life. It's significant for the patients to be detected and treated early, therefore they will have better vision and longer life. The treatments of choroidal metastasis are developing quickly. Both the vitreous cavity injection of targeted drug and gene therapy are hot topics of research. This paper summarizes the etiology, development, diagnosis and treatment of choroidal metastasis nowadays.

• KEYWORDS: choroidal metastasis; symptom; treatment
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PRIMARY DISEASE

Choroid has rich blood supply and high blood flow, the pathogen in blood can spread easily to choroid, so choroid is the most common ophthalmic part for metastatic disease. In the 950 eyes of 520 patients with ocular metastatic carcinoma, 88% of the patients were choroidal metastasis[1]. The first case report of choroidal metastasis was in 1872 by Perls[2]. Choroidal metastasis mainly occured in 40-70 years old people, and more in female than male, it happened in the left eye more than the right, choroidal metastases could not only happen monocular but also binocular. Breast cancer metastasis was the most common (40% - 53%)[3], lung cancer located in the second (20% -29%)[1,4]. In male the most common primary disease was lung cancer, and breast cancer in female[5]. Besides lung cancer and breast cancer, the source of cancer could be classified into: retroperitoneal leiomyosarcoma[6], tendon and aponeurosis[7], submandibular gland[8-9], testis[10-11], digestive tract[12-15], mediastina[16], thyroid[17-21], chondroma sarcomatosum[22], ovary[23], bladder[24], renal cell[25-27], choroidal melanoma[28].

Loss of vision and defect of visual field were the most common symptoms[6]. Other symptoms included: eyes flash, muscae volitantes[29]. At the same time a few people were asymptomatic[1,30]. Choroidal metastases could grow rapidly and compressed the ciliary nerve, the patients might have headache and ophthalmodynia.

SUPPLEMENTARY EXAMINATION

A diagnosis of choroidal metastasis was based on the patient's clinical history, symptom and some other supplementary examination.

Ophthalmoscope and Imaging

Having inspected with binocular indirect ophthalmoscope: vitreous body mostly appeared normal. Most of the choroidal metastases were located posterior to the equator(92%), 80% of them located between the equator and the macular, 12% of them located in macular area[1]. Choroidal metastases always appeared as a yellowish white or grayish yellow, roundness, base broad and sessile swelling mass under the retina[1,6,31]. Exudative retinal detachment[13,20,32] and retinal hemorrhage[33] could also be seen in choroidal metastases. Sometimes pigment spots existed on the surface of the tumor, there was no pigment inside the tumor[34]. Different primary diseases had different signs, the choroidal metastasis of lung cancer was a solitary choroidal mass, which was of great thickness[6,31], the choroid metastasis of breast cancer were multiple and flat[32,35-36]. Ultra wide-field imaging can record the growth of the choroidal metastasis on peripheral retina and

the related serous retinal detachment accurately[37].

Ultrasonography

Choroidal metastasis appeared irregular internal reflection, disparate amplitude, reduction of sound attenuation and inexistence of the locomotor in A-scan ultrasonography[38]. B-scan ultrasonography was a significant accessory examination but not specificity. The ultrasonic image could be classified as: flat, hemispherical, flat and hemispherical and double arc. The tumor located along the choroid, impenetrated the Bruch's membrane, it had smooth surface. The internal echo distribution was uniform or uneven, the front echo was more, the back echo was less, and the sound attenuation was significant. It might have choroidal depression syndrome, dig hollow phenomenon, retinal detachment and strip echo in the vitreous. We can use B-scan ultrasonography to measure the change of the tumor repeatedly. Wolff-Korman *et al*[38] suggested to use B-scan ultrasonography to quantitative assessment the tumors' progression and outcomes. The Color Doppler showed different range of hyperechoic bulge. Color Doppler Flow Imaging (CDFI) showed diffuse patchy, punctate or branched bloodflow signals inside the tumor, all of them were arterial frequency spectrum. The vascular forms could hardly been seen inside the shallow uplifts. Blood flowed velocity and resistance index increased of the central retinal artery. No abnormal blood flow signal was found in the ophthalmic artery and the posterior ciliary artery[39].

Computerized Tomography Computerized tomography (CT) often shows irregular thickening of the inner wall of the eye ball and inhomogeneous density mass, retinal detachment is always accompanied. If the tumor is small, the CT display is not obvious.

Magnetic Resonance Imaging Magnetic resonance imaging (MRI) has different expression signals for retinal detachment and mass, so for the diagnosis of choroidal metastasis effect MRI is better than that of CT. On T1-weighted images the vitreous appears low signal, the tumor appears isointensity and the exudate appears high signal. On T2-weighted images the tumor often shows hyperintensity[40].

Optical Coherence Tomography Spectral-domain optical coherence tomography (SD-OCT) had provided additional useful information for clinical diagnosis: a pattern of hyperintense irregular spots in the context of the photoreceptor layer and in the retinal pigment epithelium, subretinal fluid, and marked irregularity of the retinal pigment epithelium with thickening and gross undulation. They emphasize the central role of SD-OCT among instrumental imaging procedures and for final successful diagnosis[41]. OCT best revealed elevation of the RPE and retina, RPE thickening and folds, and retinal detachment[42]. During the time of treatment the improvement of neuroepithelium detachment in SD-OCT preceded ultrasonography[43]. SD-OCT with enhanced depth imaging (EDI SD-OCT) could observe the morphological changes of the choroid, and measure the changes of choroidal thickness. It was more sensitive than other instrumental equipment when being used to test the minor mass in the posterior pole[44-45]. 3D-OCT could show the progress of retinal pigment epithelium[32]. Swept source optical coherence tomography (SS-OCT) was a convenient method for precise, early-stage detection of choroidal metastatic lesions, involving assessment of tumor response, and for regular follow-up studies[14].

Fluorescein Angiography Fluorescein angiography showed choroidal delayed filling at the early phase, leakage of fluorescence and hyperfluorescence of opti at the late phase[45]. It can be used during the follow-up.

Indocyanine Green Angiography Indocyanine green angiography (ICG) is a well-known ancillary test for choroidal diseases. The images of the metastatic lesions was characteristic. In the research of Krause *et al*[46], the mean tumor height was 3.7 mm (2.0-9.0). Both the tumors' surface and the background were stained. 13% of the tumor showed vascular inside. 89% of the choroidal melanomas showed a blockage of the background staining. ICG do great contribute to the diagnosis, treatment and follow-up for choroidal metastasis.

Autofluorescence Autofluorescence (AF) imaging revealed hyperautofluorescence in areas of focal pigmentation and subretinal fluid with hypoautofluorescent margins corresponding to OCT evidence of retinal pigment epithelial (RPE) thickening and subretinal fluid. Loss of RPE was AF imaging hypoautofluorescent. AF images changed with tumor growth. AF imaging best defined surface characteristics and tumor margins. AF imaging hyperautofluorescence correlated to focal hyperpigmentation, subretinal fluid, and advancing tumor edges. AF imaging revealed unique tumor characteristics of choroidal metastasis[42].

Fine Needle Aspiration Biopsy Histopathology can confirmed tumor malignancy, tissue origin and classification[6,21,47-49]. But invasive procedures may risk tumor seeding. Six months after the fine needle aspiration biopsy, two tumor masses were noted over two of the sclerotomy wounds of the left eye, pathology showed the same to the primary disease[32].

Gene Diagnosis Gene diagnosis can clarify the diagnosis and guide therapy. The sequence of gene mutations can be measured. In Shimomura *et al*'s[29] research of choroidal metastases of non-small cell lung cancer (NSCLC), genetic an exon 19 deletion mutation (delE746-A750) of epidermal growth factor receptor (EGFR) of the transbronchial biopsy (TBB) specimens had been tested. This mutation predicts beneficial response to EGFR-tyrosine kinase inhibitor (TKI). One of the merits of first-line EGFR-TKI is the prompt and dramatic response for patients with an EGFR mutation. So they choose gefitinib as the first-line treatment. Fujiu's[50] research found a mutation of the epidermal growth factor receptor gene in exon 19 for a choroidal metastases of lung cancer.

TREATMENT

Molecular Targeted Therapy Crizotinib could successfully treated choroidal metastases from ROS1-rearranged NSCLC and ALK-rearranged[4]. And alectinib was active for ALK

rearrangement NSCLC having choroidal metastasis similar to other small molecule targeted agents such as crizotinib[51]. Epidermal growth factor receptor tyrosine kinase inhibitor (Gefitinib, Erlotinib) played an important role in molecular target therapy of lung cancer[29,52-53] and breast cancer[54]. Sunitinib could degrade choroid metastasis of renal cell carcinoma quickly[55].

Chemotherapy and Immunosuppression If the primary disease was sensitive to chemotherapy and immunosuppression, chemotherapy and immunotherapy was the preferred treatment in patients with choroidal metastases[56-57]. According to different primary tumor types to choose the corresponding drugs and methods.

Hormone Therapy Androgen deprivation therapy could regress the choroidal metastases of prostatic carcinoma[58]. Breast carcinoma was also sensitive to hormone therapy[59]. Chemotherapy, radiation therapy combined with hormone therapy was recommended[60].

External Beam Radiotherapy External beam radiotherapy (EBRT) was usually used at a dosage of 30-40 Gy, it caused tumor regression and 85% of the patients' vision improved or stabilized[61].

Brachytherapy There were two patients treated with plaque therapy and a diode laser therapy, one patient demonstrated partial regression of two choroidal metastases and total regression of one tumor, while the second one, showed total regression of all intraocular tumors. Teleradiotherapy caused irradiation neuropathy and retinopathy as complications[62]. Different from external beam radiotherapy, brachytherapy put the radioactive source on the area of the tumor, it can reduce the radiation of the normal structure. Interstitial brachytherapy has a shorter course of treatment than external beam radiotherapy, it is more convenient for patients. Interstitial brachytherapy was one of the effective therapy for choroidal metastases[1].

Photodynamic Therapy Nine choroidal metastases in 8 eyes were treated with 1 (8 tumors) or 2 (1 tumor) sessions of photodynamic therapy (PDT). All 9 tumors were associated with shallow subretinal fluid. After PDT, complete control with resolution of subretinal fluid was achieved in 7 tumors (78%), with mean tumor thickness reduction of 39%. Two tumors failed to respond to PDT. Improvement or stabilization of vision was achieved in 7 eyes. Photodynamic therapy - related complications included intraretinal hemorrhage in 1 eye[63]. Photodynamic therapy worked probably by damaging the new vessels within the choroidal metastasis. However, as PDT does not target tumour cells, it is possible that some of these cells may survive after PDT and later cause local recurrence. So close follow - up after treatment is very important[64]. Photodynamic therapy can be an effective way for the treatment of choroidal metastasis. PDT is not recommend as a standard treatment for choroidal metastasis[65].

Transpupillary Thermotherapy In a study of 59 eyes with choroidal metastasis managed with time temperature transformation curve (TTT) as the primary treatment, 71% of eyes showed regression or inhibition of growth, while 7% showed progression over a follow-up period of 15 mo[66]. Instead of usual high laser intensity, three applications of TTT, 400-mW power, 3-mm size, and 1-minute duration, were performed over the tumor mass. Repeated treatment with the same regimen was performed after 1wk. Visual acuity improved 2mo after treatment. The disappearance of subretinal fluid over the fovea was noted by fluorescein angiography 2mo after laser treatment and remained stable until the end of follow - up. Improvement of visual acuity and cessation of fluorescein leakage in the tumor showed that subthreshold (*i.e.* biomicroscopically invisible laser effect) TTT served as an effective treatment modality in the early resolution of macular subretinal fluid in choroidal metastasis. Multiple sessions of subthreshold TTT are safe to apply very close to the macula[67].

Intravitreous Injection Recently, Bevacizumab and ranibizumab are the main drug for injection. Some research suggests that Bevacizumab is effective to choroidal metastases[26]. Intravitreous inject Bevacizumab Combined with chemotherapy or radiation therapy might have a better effect. On the contrary, Bevacizumab had no effect on choroidal metastases[68-69]. Ranibizumab had better tissue penetration and inhibitive effects of neovascularization, it taked effect on choroidal metastases[70]. Intravitreous injection was not recommended as a primary treatment for choroidal metastase.

Other Treatments Combined with other standard treatments indocyanine green mediated photothrombosis (IMP) was an effective way for the treatment of choroid metastasis[64]. Radical mastectomy combined and hormone therapy combined with Gamme Knife Radiosurgery, the choroidal mass disappeared and the patient kept good vision during the one year follow-up[71].

An accurate diagnosis based on the patients' clinical symptoms, medical history, doctors' examination and necessary accessory examinations is the most important part during the treatment of choroid metastases. Systemic therapy combined with some other sensitive local treatments were commonly used. Different origin of the metastases fit different therapy, some need to choose thoughtfully.

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