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Ocular metastases

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Abstract

The eye is a rare site for disseminated malignancy because of the absence of a lymphatic system. Metastases to the ocular structures occur by haematogenous spread and therefore the parts of the eye with the best vascular supply are most likely to be affected. Many patients with Stage 4 carcinomatosis (distal metastatic spread) already have a history of a previous primary cancer. However, this is not always the case for lung cancer as this can metastasise early to the uveal tract and therefore the ophthalmologist may be the first to discover the presence of terminal metastatic disease. Broadly speaking, treatment options are focused on improving the patients' quality of life if visual acuity is threatened. Long-term side effects of treatment need to be considered as systemic cancer treatments and therefore patient life expectancy is improving. In this manuscript, presented at the Cambridge symposium 2012, the diagnosis and challenges involved in the management of ocular metastases are presented.
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Introduction

Despite the fact that ocular metastases are reported to be the most common intraocular tumour, they are rarely seen while the patient is alive. This is because much of the data regarding the incidence of ocular metastases is based on autopsy data where the microscopic detection rate is reported; other percentages are based on old publications that are now outdated.[1,2] The estimated incidence of ocular metastases in the United States is 20 000 per annum. Most of these patients are never seen by an ophthalmologist. It has been proposed that this is because patients have no visual symptoms or perhaps do not complain of visual disturbance because they have systemic medical problems of greater severity. Hence, some have questioned the need for ophthalmic screening of all patients with metastatic disease. In 2007, Fenton and Barak both reported a 0% incidence of choroidal metastases following ophthalmic screening of asymptomatic British patients with metastatic breast carcinoma.[3,4] Only 2% of patients suffering disseminated lung cancer were found to have asymptomatic choroidal metastases.[4] They argued that the high cost of an ophthalmic screening programme could not be justified with such a low detection rate. Therefore, there is now a strong argument not to screen for asymptomatic choroidal metastases. Furthermore, a recent report suggests that the incidence of microscopic metastases has not changed and that the incidence of clinically detectable intraocular metastases has fallen from 4.7 to 1% owing to improved cancer therapy.[5]

However, some unfortunate patients do present with visual loss or metamorphosia. It is these patients who reach our ophthalmic community and often require the opinion of an Ocular Oncologist. Management of these patients is multidisciplinary involving shared care with local medical or radiation oncologists, palliative care, and other named cancer services.

Clinical features

Metastatic disease can present in any part of the eye or orbit but the uveal tract is the most common structure involved. Metastatic disease to the eye is by haematogenous spread, therefore the most frequent location affected is the perimacular choroid because of the increased vascular supply to this area. Iris and ciliary body metastases are present in 10% of cases. In this location, patients present with chronic anterior uveitis, episcleritis, or raised intraocular pressure owing to iris neovascularization or trabecular meshwork block from metastatic deposits. The presumed inflammatory disease or raised intraocular pressure is resistant to treatment. Creamly pale

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and sometimes pink iris nodules can be seen (Figure 1a). Other parts of the eye, such as the retina, optic disc, vitreous, and conjunctiva, can be affected but this usually occurs when there is already uveal tract involvement.

Choroidal metastases are associated with an unusually large amount of subretinal fluid for their size. The patient may present with a complete retinal detachment and a mass is only seen clearly on ocular ultrasound (Figure 1b). This contrasts with melanoma, which needs to be of a significant size before an exudative retinal detachment is seen. Many choroidal metastases are asymptomatic unless the macula is directly involved. They tend to be pale and often have a characteristic leopard spot appearance from retinal pigment epithelial change on the surface (Figure 1c). Lipofuscin from poorly functioning retinal pigment epithelium can be seen on the surface of metastatic deposits as well as ocular melanoma. Fluorescein angiography of a metastatic deposit reveals hypofluoresence in the arterial phase followed by late hyperfluorescence with no pooling of dye. ICG is useful to differentiate a choroidal haemangioma from a metastatic deposit; however, the most helpful investigation is an ocular ultrasound. B scan ocular ultrasound combined with Doppler blood flow velocity is performed on every patient referred to the Ocular Oncology service with an intraocular mass lesion. Metastases are typically placoid shaped with an undulating surface and show medium to high blood flow velocity. There are always exceptions to the rule, as lung metastases to choroid may mimic the mushroom or collar stud shape of choroidal melanoma. Most ocular metastases are indistinguishable in terms of the original primary tumour; however, certain primary tumours are associated with a particular metastatic appearance. Carcinoid metastases in the choroid appear orange as do thyroid metastases. Renal metastases are more likely to produce intraocular haemorrhage. A solitary ocular metastases from cutaneous melanoma is pigmented and difficult to distinguish from a primary choroidal melanoma, although retinal and vitreous pigmented seeding is a helpful indication that the pigmented choroidal tumour may be a secondary.

Investigations

Most patients presenting with ocular metastases already have a history of treated primary cancer. The most common primary tumours to metastasise to the eye are from breast (47%), lung (21%), and the gastrointestinal tract (4%).[6] In some cases, the patient may have no other symptoms and the Ocular Oncologist may be the first doctor to inform the patient that after years of remission they now have stage 4 disease.[7] In my personal experience, it tends to be metastatic breast cancer that can result in such diagnostic shock to the patient and oncologists previously involved in that individual's treatment. On the other hand, primary adenocarcinoma of the lung can present for the first time with ocular metastases in up to 50% of cases. This is a staggering statistic that should be remembered in any individual with a significant history of smoking even in the absence of any respiratory symptoms.[8] The mainstay investigation should be a CT chest. The hunt for a systemic primary cancer is often best performed in conjunction with a medical oncologist as once the tumour is found, the patients' treatment can be streamlined more efficiently. We perform a full-body PET/CT in all patients when metastatic disease is suspected; this is a very helpful investigation for lymphoma and melanoma, which is metabolically active and therefore shows good uptake of FDG. When lymphoma or metastatic breast cancer is suspected, an MRI of the brain is an important investigation because cerebral and intraocular cancers often coexist, or follow each other. Patients presenting with metastatic cutaneous melanoma may have a history of an unusual mole, which subsequently disappeared, a spontaneously regressed cutaneous melanoma. For the vast majority of patients, the primary cancer can be discovered very quickly using the above approach; we rarely find the need to perform in intraocular biopsy.

However, in 10% of cases, the primary systemic cancer is never discovered and therefore a tissue diagnosis is necessary. The surgical approach depends on the location of the tumour. Most histopathologists prefer a block of tissue to examine as the surrounding structure of the tumour often aids in the diagnosis as apposed to a fine needle aspirate, which can sometimes result in a diagnostic challenge. Therefore, whenever possible, we try to perform a transcleral or transcorneal approach. The other advantage of this surgical approach is the larger amount of tissue recovered for examination. Transretinal biopsy following a pars plana vitrectomy will also preserve the histological structure of the biopsy specimen. Fine needle aspiration biopsy, however, is sometimes the only approach possible for small posterior choroidal masses. A transcleral or pars planar technique can be used (Figure 1d). The patient should be warned of the risk of inadequate yield to make a diagnosis and difficulty in interpretation of the results by a cytopathologist. This particularly is a concern for tumours <2 mm in thickness.[9] All techniques carry a risk of intraocular haemorrhage and hence visual loss, which is why I prefer to determine the diagnosis by my non-invasive methods first.

Finally, another important diagnostic clue is the behaviour of a metastatic deposit. Ocular metastases tend

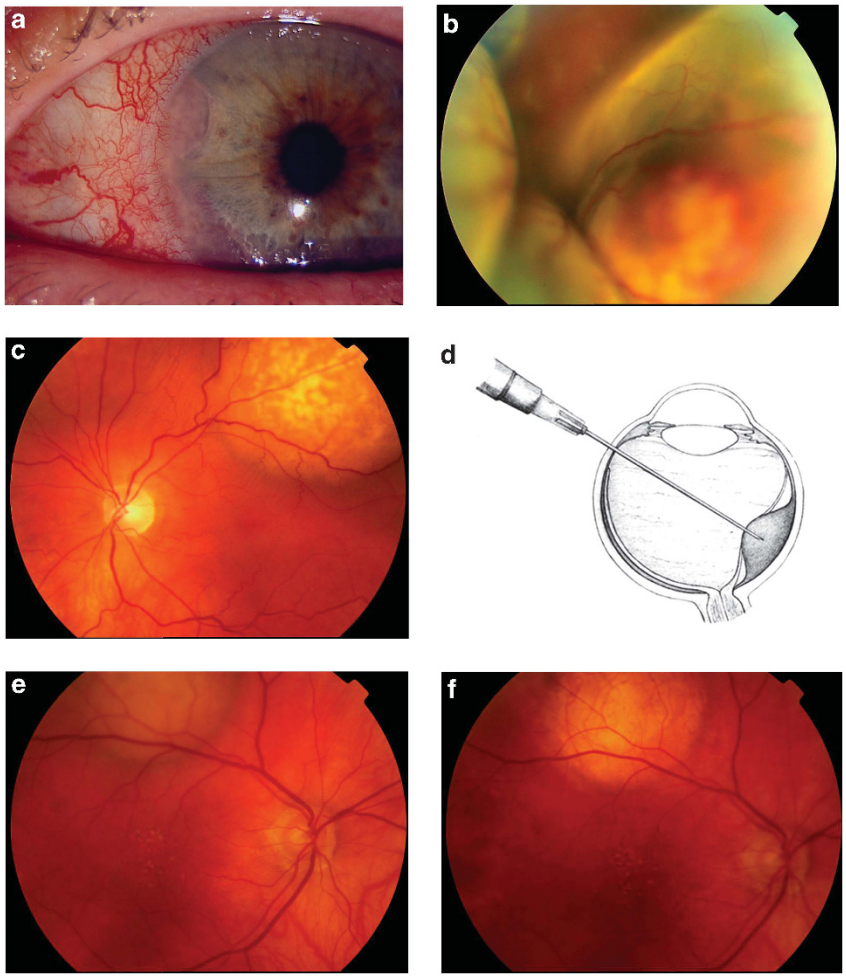

Figure 1 (a) Iris metastases seen in a patient undergoing treatment for a chronic episcleritis. The lady had a history of ductal adenocarcinoma of the breast; investigations revealed disseminated metastases with intracranial involvement. (b) Leopard spot retinal pigment epithelial change seen over the surface of a posterior polar choroidal metastases. A primary carcinoma was subsequently discovered in the wall of the oesphagus. (c) Subtotal exudative retinal detachment associated with a solitary choroidal metastasis. The patient had no previous history of malignancy but investigations revealed metastatic non-small-cell carcinoma of the lung. (d) Pars plana fine needle aspiration biopsy. Passage of the needle through the vitreous gel reduces the risk of extra-ocular seeding. (e) Isolated choroidal metastasis from undiagnosed primary ductal carcinoma in a man. The tumour was oestrogen receptor positive and responded to systemic tamoxifen. (**f**) Two years later, the breast metastasis regressed to a flat area of choroidal atrophy.

to show rapid growth, often doubling in size in a few weeks. In contrast, a primary amelanotic melanoma will not change for many months. This rapid change in tumour appearance can be a very helpful diagnostic sign when systemic investigations fail to reveal the primary tumour.

Treatment

The aim of treatment is to restore visual acuity and therefore improve the patients' quality of life for their remaining life span. The average survival following a diagnosis of uveal metastases is 7 months.[10,11] This fact is important when deciding between treatments. There is a wide range of management options for intraocular metastases. The choice of treatment depends on the extent, location, and origin of the metastases but also on the patients' general well-being and life prognosis.

Lung and breast metastases are radiosensitive and also happen to be the most common cancers to metastasise to the uveal tract. Radiotherapy is the most frequent treatment employed for these tumours. This is typically from an external source, such as X-rays, with or without lens sparing techniques. If the retinal pigment epithelial function is still intact, subretinal fluid resolves with restoration of visual acuity. Wiegel *et al*[10] reported that treatment was successful in restoring or stablising vision in up to 86% of patients following external beam

radiotherapy. Proton beam radiotherapy has also been used,[12] but it is difficult to justify using this expensive treatment when there is no treatment advantage over external beam radiotherapy with a linear accelerator. External radiotherapy is time consuming as most treatments are fractionated 15–20 times over 3 to 4 weeks; this can pose logistical difficulties for patients who are very unwell. Although in these circumstances, many radiation oncologists will significantly reduce the fractionation rate. The major advantage of external beam radiotherapy is that it is widely available, hence these treatments do not need to be performed in an Ocular Oncology centre. On the other hand, internal plaque brachytherapy with iodine or ruthenium can be very effective for small solitary choroidal metastases.[13,14] It can be completed in only a few days, which is helpful for patients with a limited life expectancy.

Many metastases respond to systemic chemotherapy, particularly the taxans used in the treatment of breast cancer. This may explain why screening fails to detect the presence of ocular metastases in patients with metastatic breast cancer.[3] We have seen successful regression of choroidal metastases in a man following treatment with tamoxifen for an oestrogen receptor-positive breast cancer (Figures 1e and f).[15] This has also been reported with the new aromatase inhibitors, which have been developed for post-menopausal women with oestrogen receptor-positive breast cancer. Manquez *et al*[16] reported that systemic aromatase inhibitors were effective in treating choroidal metastases from breast cancer in 59% of patients, many of whom did not previously respond to tamoxifen. The Ocular Oncologist is able to monitor the response to systemic treatment most effectively for the medical oncologists, as regression of a uveal metastasis can be observed directly, unlike metastases in other parts of the body. The disadvantage is that regression of ocular metastases is often slow following chemotherapy, and therefore if vision is threatened owing to extensive subretinal fluid at the macular then it is preferable to use another treatment modality, such as radiotherapy or laser.

Photodynamic therapy has recently proved to be an effective laser treatment for shallow well-circumscribed choroidal metastases[17] and solitary retinal metastases.[18] Kaliki *et al*[17] at the Wills Eye Hospital recently published their success with PDT treatment of breast cancer metastases to the choroid in seven out of eight cases. Photodynamic therapy has also been used successfully in a case of choroidal metastasis from carcinoid tumour that was refractory to chemotherapy and radiotherapy.[19] Treatment is performed using the standard TAP protocol (600 mW/cm^2 delivered over 83 s) following intravenous verteporfin infusion.[17–19] The resolution of subretinal fluid and restoration of visual acuity is a rapid process that occurs over the next 6–8 weeks. However, long-term benefit of this treatment remains unpublished.

Intravitreal anti-VEGF has also recently been effective for the treatment of choroidal metastases. This has been demonstrated for adenocarcinoma of the lung and colon metastatic to the uveal tract.[20,21] A dose of up to 4 mg of bevacizumab was administered;[21] however, 1.25 mg also appears to be effective. The authors demonstrated that this treatment was best for small, circumscribed uveal metastases in the absence of an exudative retinal detachment.[21] This discovery is not a surprise as the drug bevacizumab (Avastin) was originally developed for the systemic treatment of gastrointestinal cancer. The injections may be repeated on a 4–6 weekly basis similar to the treatment of choroidal neovascular membranes in macular degeneration. Both anti-VEGF and PDT are suitable treatments for patients who are not able to withstand multiple daily visits to hospital.

The repertoire of treatment options for metastatic disease to the eye is increasing. In addition, patients with metastatic disease are living longer owing to improvements in systemic treatments, such as immune modulatory drugs and targeted chemotherapy of cancer. Therefore, it is important that the potential medium to long-term side effects of any new ocular treatments are considered. Further publications are needed to establish the role of PDT and anti-VEGF therapies. Until that time external beam radiotherapy remains the most established treatment for vision threatening metastatic disease to the eye.

Conflict of interest

The author declares no conflict of interest.

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