Unexplained Visual Acuity Differences Between Eyes Should Lead to a Thorough Examination to Exclude Uveal Melanoma: A Case Series of Clinical Features

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Abstract
Uveal melanoma is the most common primary intraocular malignancy, accounting for 80% of all eye malignancies in adults. Uveal melanoma has a high tendency to metastasize and prompt recognition and onward referral of suspected uveal melanoma is paramount to a good prognosis. An unexplained visual acuity differential between eyes should prompt a thorough examination to exclude uveal melanoma. We present a case series of patients who presented with uveal melanoma and review etiology, characteristics and management.

Introduction
Uveal melanoma is the most common primary intraocular malignancy, representing approximately 80% of all eye malignancies in adults, commonly having asymptomatic presentation. Prompt recognition of melanoma features on examination and ophthalmological investigations is paramount for appropriate treatment. We present a case series of patients who were diagnosed with uveal melanoma over a three-year period and were followed up for a further 3 years.

Methods
A retrospective review of clinical records was conducted for patients reviewed in the Ophthalmology Department in Great Western Hospital from October 2014 to October 2017. Patient demographics, presenting symptoms, investigations, diagnosis and co-morbidities were collected, including post-diagnosis clinical course and complications. Shapiro-Wilk test was performed to assess normality of data. Continuous variables are expressed as mean ± SD for normally distributed data and median (range) for those without a normal distribution, and compared using the independent samples t-test and Mann–Whitney U test respectively. P < .05 was considered as statistically significant. All analyses were carried out using GraphPad Prism 6 (GraphPad Software, San Diego, California, USA).

Results
A total of thirteen patients were diagnosed with uveal melanoma in the 3 years between October 2014 and October 2017. The median age at diagnosis was 71 years (range 43 - 88), with a mean of 66. Eight patients were female (61.5%) and five patients were male (38.5%). Co-morbidities at diagnosis included hypertension (23.1%), hyperlipidemia (30.8%), diabetes mellitus (23.1%) and ischemic heart disease (30.8%). Four patients (30.8%) had previously treated cancer; namely: prostate adenocarcinoma (2/13, 15.4%), skin squamous cell carcinoma (1/13, 7.7%) and breast adenocarcinoma (1/13, 7.7%).

Five patients had a tumor in the right eye, eight patients in the left eye and no patients had bilateral lesions. All patients were Caucasian with five patients (38.5%) from Swindon Town, four patients (30.8%) from Marlborough, and the rest of the patients from various areas in the county of Wiltshire. There was no significant north-south gradient in our cohort.

Eight patients (61.5%) were asymptomatic at presentation and were diagnosed following detection of suspicious fundus lesions by community optometrists (n=5, 38.5%) and ophthalmologists in an outpatient setting (n=2, 15.4%). Five patients (38.5%) presented directly to the ophthalmology emergency service with eye symptoms in the form of a visual field defect (n=2, 15.4%), vision loss (n=2, 15.4%) or a gradual blurring of vision (n=1, 7.7%).

Visual acuity at presentation was 0.2 log MAR units (0 - 1.2) for the affected eye and 0.04 log MAR units (0 - 0.22) for the contralateral eye. A Wilcoxon Signed-Ranks test indicated that median visual acuities between the ipsilateral and contralateral eyes were significantly different (P<.05, Figure 1).

Representative fundus photographs of uveal melanoma findings in the macula (Figure 2A), optic nerve (Figure 2B) and extreme periphery (Figure 2C) are shown in Figure 3.
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B-Scan Ultrasonography was completed in the department to further define the lesion prior to onward referral. Other features found at presentation included exudative retinal detachment (30.7%), uveitis (7.7%) and vitreous hemorrhage (7.7%). Figure 3A shows a longitudinal B-Scan with the probe directed from the infero-temporal direction demonstrating a supero-nasal mass with a thickness of 9.13mm and diameter of 14.58mm that is iso-echoic to the choroidal tissue. Figure 3B shows a longitudinal B-Scan with the probe directed from the superior direction in the same patient demonstrating an inferior exudative retinal detachment. Fluorescein angiography (FA) was completed in a subset of patients to further define the lesion. Figure 4 shows FA completed on patient with a choroidal mass near the macula demonstrating hypofluorescence in the pigmented areas, surrounded by hyperfluorescence that commences at the arterial phase (Figure 4C) and increases well into the recirculation phase (Figure 4F).

Median range of follow-up was 33 months (10 - 37). The most common complication from treatment was radiation maculopathy (n=3, 23.1%), which was managed by intravitreal bevacizumab injections (5 injections, range: 4 - 8). Median visual acuity at last follow-up was 0.22 log MAR units (0 - 4). A Wilcoxon Signed-Ranks test showed that median visual acuities at presentation and at last follow-up were significantly different (P<.05).

Two patients died as a direct consequence of uveal melanoma, one due to local spread and the other secondary to metastatic liver cancer. One patient developed widespread metastases, which were proven histologically to be secondary to pre-existing prostate adenocarcinoma. Of the remaining patients (10/13, 76.9%) none had evidence of local or extra-ocular metastases at last follow-up.

Discussion
We report a case series of 13 patients with uveal melanoma who were diagnosed over a three-year period in Wiltshire. Wiltshire has a population of approximately 470,000 of a predominantly Caucasian background,\(^2\) leading to an incidence
rate of 10 cases per million. International incidence figures vary widely from 1 to 8 cases per million in Caucasians, with a North-South gradient and correspondingly higher incidence rates in Northern Europe.\(^3\) Latitude has been suggested as a surrogate of increased light exposure as a positive risk factor or a confounder of darker eye and skin pigmentation as a protective factor. In our cohort, similarly to previously published studies in the United Kingdom,\(^4\) a North-South gradient was not discernible. Variability between local authorities within the United Kingdom has been attributed to race differences, whereby Afro-Caribbean and Asian ethnic backgrounds are protective factors.

Risk factors for uveal melanoma include light-colored irises, and conditions such as congenital ocular melanocytosis, melanocytonoma, and neurofibromatosis. Age is a widely recognized risk and prognostic factor,\(^5\) with increasing age conferring increased risk for uveal melanoma, reaching a plateau at 75 years of age. In our cohort a bimodal distribution with respect to age was visible, with peaks at 50 and 80 years of age, however this may be secondary due to the small sample size. Reported mean age at diagnosis of uveal melanoma is 58 - 61 years of age.\(^6\) In this series, the mean age of diagnosis was 66 years.

Two of the female patients had a past medical history of breast carcinoma, potentially highlighting the importance of the genetic association between the BRCA Associated Protein-1 (BAP-1) gene defect and the female gender. The incidence is high enough to justify targeted additional genetic screening for patients of the Caucasian race who present with choroidal naevi and have either family history of uveal melanoma or females with breast carcinoma.

The diagnosis of choroidal melanoma is usually made on basis of clinical examination; the lesion classically appears as a pigmented dome-shaped mass. In our cohort the majority of the patients were asymptomatic, so early detection remains an important determinant for the prognosis in view of prompt treatment. It is important to note that there was a significant difference in visual acuity between eyes at presentation. The presence of an unexplained visual acuity differential between eyes should prompt a thorough examination to exclude uveal melanoma.

Features most suggestive of malignancy include low internal reflectivity of the mass on B-scan ultrasound, the presence of sub-retinal fluid, lipofuscin deposits, photoreceptor inner-outer segment disruption and documented growth. Other diagnostic tests include fluorescein angiography, which highlights the dual circulation pattern of the lesion, and fundus auto-fluorescence in which hypo-pigmented lesions exhibit hyper auto-fluorescence while pigmented lesions appear as hypo auto-fluorescent areas. Biopsy can be helpful if confirming diagnosis and has the advantage of providing cytology and genetic testing to help guide risk of distant spread. Trans-vitreal retina-choroidal biopsy is becoming a more reliable method for obtaining adequate amounts of tissue for genetic testing compared to fine needle aspiration cytology with reduced risk of seeding.

Management is highly patient-dependent in uveal melanoma. Observation alone may be suitable for small tumors with no documented growth, aiming at striking a balance between exposing the patient to risk of metastases and over-treating stable lesions that could result in significant ocular morbidity and visual loss.\(^7\) Eye-conserving management options include

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<tr>
<th>No.</th>
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transpupillary thermotherapy using diode laser, a suitable technique for small lesions with thickness less than 4 mm. Radiotherapy options include brachytherapy, charged-particle radiotherapy and proton beam therapy. Brachytherapy involves suturing a radioactive plaque onto the sclera overlying the tumor and while suitable for small-to-medium sized tumors, is associated with increased toxicity to the surrounding tissue. In our series, all the patients that received plaque radiotherapy developed radiation maculopathy. Presentation was variable, similarly to the literature, either affecting the superficial retina with cystoid macular edema or the deeper retinal layers with significant sub-retinal fluid. Maculopathy was effectively managed with a median number of 5 intravitreal bevacizumab injections, that resulted in anatomical and functional recovery. For tumors that are too large for plaque brachytherapy or in positions where plaques cannot be placed directly, such as the optic disk and fovea, charged-particle radiotherapy can be used, a technique with a sharp reduction in radiation beyond the targeted area. Stereotactic proton beam radiotherapy utilizes a proton beam to deliver radiation to the tumor site, and is a particularly helpful option for large tumors. Trans-retinal or trans-cleral endoresection represent eye-preserving surgical approaches, which while being associated with improved retention of visual acuity when compared to brachytherapy, have higher recurrence rates. With the development of eye-conserving therapies, enucleation is now reserved for cases with the worst visual prognosis such as peri-papillary melanoma or tumors causing retinal detachment. Prosthetic eye services hold a central role in post-enucleation care allowing comfort and improvement in patient-reported outcomes.

Summary
Prompt recognition and onward referral of suspected uveal melanoma is paramount to a good prognosis. Optometrists provide an invaluable resource for screening and annual visits to the opticians are essential in the population above 50 years of age. Any unexplained visual acuity differences between eyes should prompt a thorough examination for uveal melanoma.

References

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