



Treatment of *Metarhizium* fungal keratitis in the United Kingdom

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Received: 5 April 2018 / Accepted: 5 April 2018 / Published online: 11 June 2018
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Introduction

A 22-year-old female patient presented with pain and reduced vision in her right eye for the past few days. She had a three-year history of monthly soft contact lens wear and a past medical history of anxiety managed with citalopram. She was otherwise well. The patient worked as a veterinary student, reported to showering in her contact lenses and denied a history of trauma. On presentation right CDVA was 20/120 with spectacles (pinhole 20/30) and 20/16 on the left. The conjunctiva was injected on the right. In the mid peripheral cornea there was a 4 mm by 4 mm epithelial defect within which there was a dense infiltrate measuring 2.2 mm by 1.7 mm. The anterior chamber was quiet. A diagnosis of microbial contact lens related keratitis was made.

A corneal scrape was performed, and levofloxacin 0.3% drops were started hourly day and night. On review day three, right CDVA had improved to 20/80 (pinhole 20/30) and the eye felt more comfortable. However, the infiltrate and epithelial defect had increased in size. Cefuroxime 5% drops were added hourly day and night. On review day 5, the visual acuity had improved to 20/40 on the right with glasses (pinhole 20/30). The right eye remained intermittently sore. On examination, the epithelial defect had increased in size to 8 mm by 8 mm, with the mid peripheral infiltrate now chalky in appearance measuring 2.5 mm by 2.5 mm. Satellite lesions were also apparent. A clinical diagnosis of fungal keratitis was made, which was confirmed by a positive culture of scanty growth of fungus from the initial corneal scrape.

The patient was admitted for treatment with voriconazole 1% hourly day and night, along with cefuroxime and

levofloxacin two hourly. Comfort improved on this treatment and the voriconazole was reduced to hourly day only. The patient was discharged on this treatment at day 7. On day 12, the right eye started to deteriorate with increased pain. Visual acuity was reduced to 20/200 on the right (pinhole 20/120). Clinical examination revealed a large endothelial plaque behind the infiltrate that had now enlarged to 3 mm vertical by 2.5 mm horizontal. A further corneal scrape was performed. This and the original scrape identified *Metarhizium* species.

Treatment was changed to topical natamycin 5% hourly day and night. The corneal ulcer and infiltrate improved rapidly on this treatment and it was tapered to two hourly by day 18. The infiltrate had cleared by day 22. Treatment was reduced to six times a day and continued with the levofloxacin four times a day. At review day 29, visual acuity was 20/80 on the right (pinhole 20/40) with full resolution of the epithelial defect. The right eye was however mildly injected and keratic precipitates were noted on the endothelium. Topical cyclosporin A 0.1% was commenced twice daily with natamycin continued six times daily.

At review day 60, right CDVA was 20/20 with glasses and the eye was comfortable. Clinically there was a 3.5 mm by 3.5 mm scar, not affecting the visual axis. The eye was white, with no epithelial defect or infiltrate and treatment was ceased. The patient was reviewed on day 75 and remained asymptomatic off all treatment with a CDVA of 20/20 and was discharged.

Discussion

Metarhizium anisopliae is a filamentous entomopathogenic fungus used worldwide as an agricultural insecticide [1]. The organism has optimal growth at 25 °C and as such has been considered safe, though has extremely rarely being implicated in human disease [1, 2]. *Metarhizium* has been implicated in a small number of cases of keratitis, sclerokeratitis and endophthalmitis. This report to our knowledge is the ninth worldwide for an ocular infection. The first

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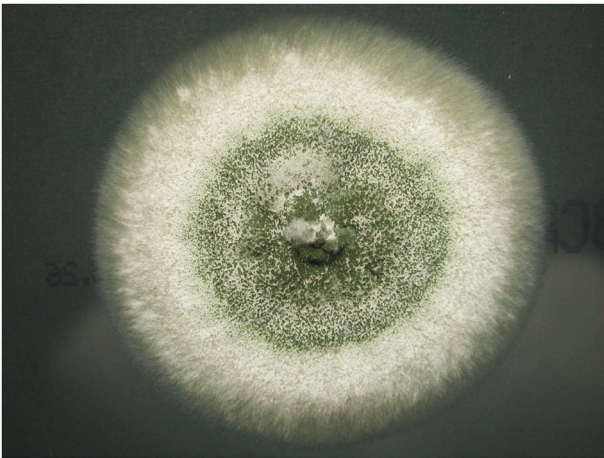


Fig. 1 Macroscopic appearance of *Metarhizium* species identified

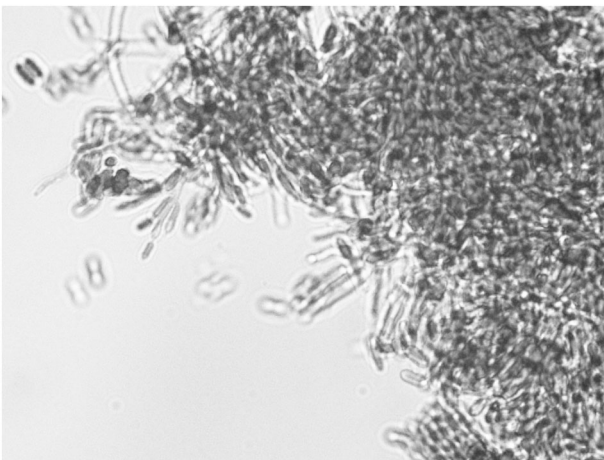


Fig. 2 Microscopic appearance of *Metarhizium* species identified

Table 1 Antifungal susceptibility reports from three *Metarhizium* keratitis case reports. MIC presented in mg/L

Reference	This report	Eguchi et al. [7]	Dorin et al. [2]
Susceptibility method	CLSI broth dilution	CLSI broth dilution	<i>E</i> -test R
Amphotericin B	Resistant [$m = 2$]	Resistant	Resistant
Voriconazole	Sensitive [$m = 1$]	Sensitive	Sensitive
Econazole	Intermediate [$m = 2$]	—	—
Itraconazole	Resistant [$m > 16$]	Sensitive	Resistant
Natamycin	Sensitive [$m = 8$]	—	—
Posaconazole	—	—	Sensitive
Fluconazole	—	Sensitive	Resistant
Miconazole	—	Sensitive	—
Micafungin	—	Sensitive	Sensitive
Caspofungin	—	—	Sensitive
Flucytosine (5-FC)	—	Resistant	Resistant

report was in 1997 from Colombia [3], then subsequent reports emerged from the United States [4, 5], Australia [6], Japan [7], France [2, 8] and Canada [9]. This is the first report in the United Kingdom. Of the previous eight cases, four implicated contact lens wear [4, 5, 7, 9], three involved ocular injection of organic material [2, 6, 8] whilst the initially described case had no identifiable risk factors [3].

Corneal scrape samples were cultured, and fungal elements identified at the North Bristol Bacteriology laboratory. Isolates were sent to the Public Health England South West Mycology Reference Laboratory for identification. The organism was identified as *Metarhizium* species. Macroscopic and microscopic images are shown in Figs. 1 and 2. Susceptibility studies were performed by CLSI (Clinical Laboratory Standards Institute) broth microdilution method M38-A2. Results are presented in Table 1 with those from the only other two ocular cases with reported susceptibilities [2, 7].

Amphotericin-B resistance has been almost universal in ocular and non-ocular *Metarhizium* mycosis susceptibility reports, indicating a possible intrinsic resistance to the agent [2]. Despite in vitro sensitivity to voriconazole in the reported susceptibilities, there was little response in our case with clinical deterioration. A similar trend was seen with progression despite voriconazole therapy delivered topically [9] or systemically [2] in other cases. It is established that for filamentous fungi particularly, in vitro MIC values indicating susceptibility do not always correlate with effective host response to treatment [10].

Natamycin was used to successfully treat three previous cases with excellent outcomes [3–5]. Conversely, two cases progressed to keratoplasty and poor outcome despite natamycin treatment [6, 7]. In the two cases where natamycin was unavailable, infection progressed to require therapeutic keratoplasty despite topical and systemic antifungals, one case with corneal perforation at day 11 of treatment [2, 9].

Natamycin 5% is employed as a first line empiric antimycotic therapy in many centres [10]. Potential drawbacks include limited ocular penetration, lack of widespread availability of a commercial ophthalmic product and restricted efficacy in yeast type keratomycoses. Empiric first-line treatment with natamycin 5% is optimal for superficial mycotic appearing infiltrates or those with filamentous elements identified on microscopy or culture [10]. In the context of *Metarhizium* species identification, this case adds support to the use of topical natamycin. This report further demonstrates clear clinical inferiority of voriconazole despite in vitro sensitivity as well as the presence of amphotericin B resistance in *Metarhizium* keratitis samples.

Acknowledgements Thanks to Dr Elizabeth Johnson and Adrien Szekely for *Metarhizium* images included in Figs. 1 and 2.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Eye (2018) 32:1792–1794
<https://doi.org/10.1038/s41433-018-0156-6>

Reversible retinal toxicity in early oral Entecavir therapy for hepatitis-B infection

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Received: 30 April 2018 / Accepted: 22 May 2018 / Published online: 22 June 2018
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We illustrate an acute retinal toxicity from oral Entecavir (Bristol–Myers–Squibb, USA) as treatment for acute hepatitis-B infection, and subsequent reversal of retinal toxicity upon stopping Entecavir with full restoration of visual functions.

Case report

A 52-year-old Caucasian male presented with unilateral sudden painless reduced vision and central scotoma of 5-day duration. Patient was diagnosed acute hepatitis-B infection 6 weeks before and was started with oral

Entecavir 0.5 mg once daily. His presenting vision was 6/15OS and 6/6OD, normal pupillary reactions, full colour-perception and no ocular inflammation. Right fundus was normal while left showed mildly hyperaemic optic disc and a central well-demarcated hypopigmented area in posterior pole (Fig. 1: 1A). Both fundus-fluorescein angiography (Fig. 1) and optical coherence tomography (Fig. 2) depicted corresponding retinal pigment epithelial (RPE) and photoreceptors abnormality. He had also established patchy central Goldmann field defects and grossly reduced full-field electroretinogram (delayed responses from both rod and cones) in OS only. Excluded retinovasculitis and satisfactory normal systemic investigations, a suspicion of drug toxicity was made. Entecavir was stopped immediately and remained off when his liver function test was also normalised. At 2-month review, his vision had reached 6/6, centre RPE hypopigmentation became indistinct. By 5 months, all visual function tests and funduscopy were fully restored (Figs. 1, and 2).

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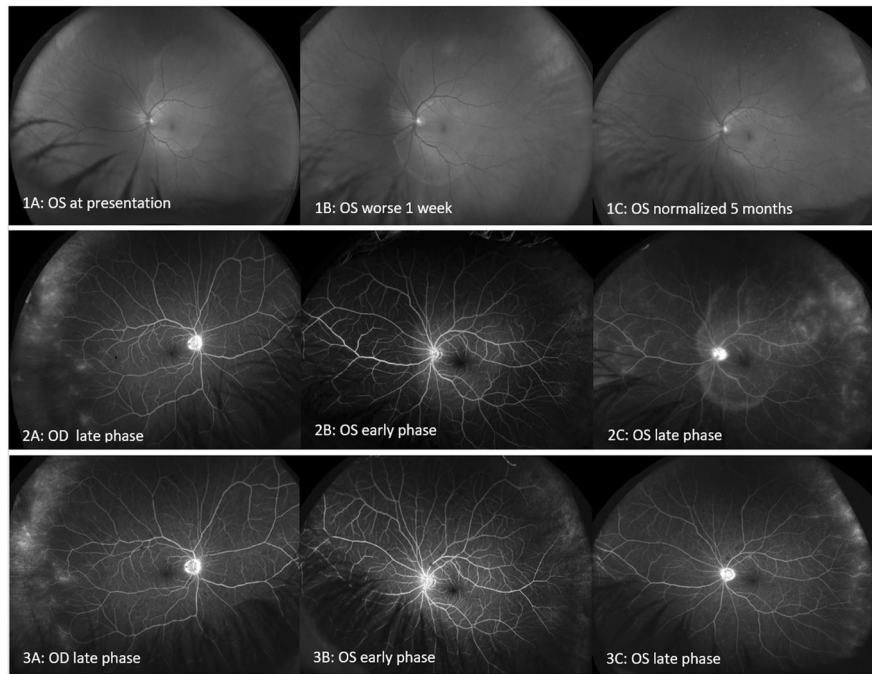
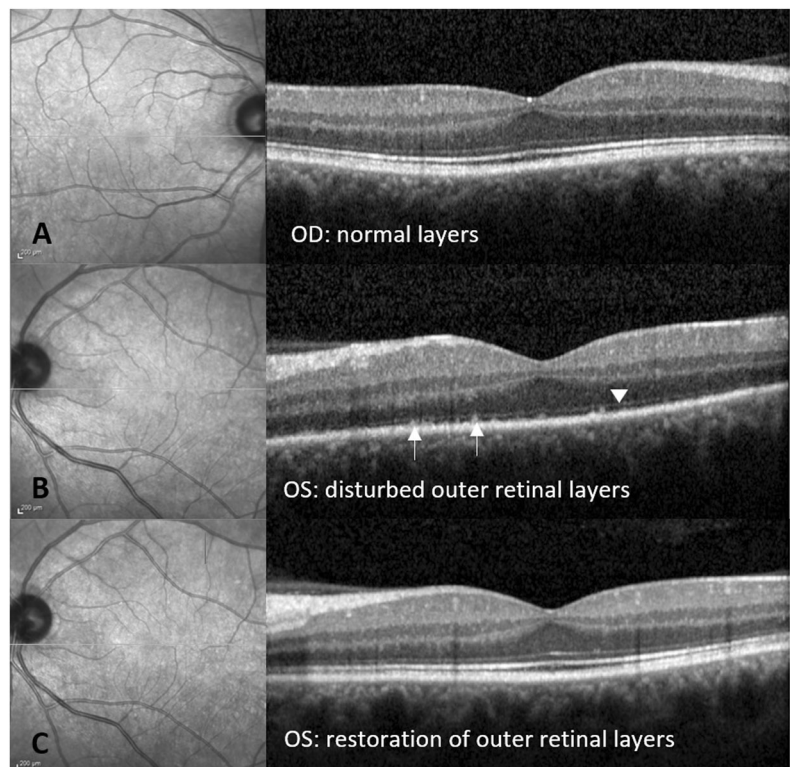


Fig. 1 Fundus photographs and fluorescein angiography (FFA). Fundus photographs of OS showed a clear demarcation of retinal pigment epithelial (RPE) hypopigmentation in posterior pole at presentation (1A). Patient's vision was 6/15 and complained of central scotoma, Entecavir was stopped at this point due to suspicion of retinal toxicity. At 1-week review, vision was worse (6/18 OS) and there was evidence of enlargement in demarcated RPE hypopigmentation area (1B). At 5-month review, patient had made a full spontaneous visual recovery in all aspects with 6/6 vision (1C). FFA at 1 week after presentation (2A–C): OD showed late-phase temporal peripheral distal venous staining and peripapillary hyperfluorescence but normal posterior pole (2A). OS showed early well-demarcated area of early RPE layer hyperfluorescence corresponding to clinical hypopigmentation (2B), and remained staining in late phase (2C). There was more intense hyperfluorescence on optic disc and wider peripheral distal venous staining. FFA at 5 months after presentation (3A–C): both eyes showed significant normalisation with some residual peripheral venous staining. OS=Left eye, OD=Right eye

Fig. 2 Optical coherence tomography (OCT) scans. At presentation, OCT showed normal retinal layers in OD (a), contrasting abnormal retinal layers in OS (b) with loss of reflectivity of photoreceptor ellipsoid zone and outer segments with intact external limiting membrane (white arrowhead), and multiple small high reflective elevations seen on RPE layer (white arrows). Repeated OCT at 5 months confirmed restoration of all retinal layers in OS (c). OS=Left eye, OD=Right eye



Entecavir is an anti-viral drug commonly used in treatment of hepatitis-B infection but there was no recognised ocular toxicity in its association [1–3]. The mechanism of retinal toxicity remains unclear with lacking histopathological studies. There was a published case report with irreversible blindness when on year(s) of Entecavir complicated by diabetic retinopathy at the time of suspected retinal toxicity [4]. Our case shared similar clinical features as their reported second eye. Notably, Entecavir drug toxicity is causing sequential rather than bilateral simultaneous eye manifestations. Our patient's left eye was profoundly involved but his right eye had not progressed more than the minimal peripheral vascular staining in late fundus photographs and fluorescein angiography phase (Fig. 1: 2A).

Our case confirmed short-term Entecavir use could cause reversible retinal toxicity upon drug cessation. Prescribing physicians and ophthalmologists should be aware of the potential retinal toxicity of Entecavir. We reported this adverse drug reaction to the UK Medicines and Health Products Regulatory Agency.

Eye (2018) 32:1794–1795
<https://doi.org/10.1038/s41433-018-0161-9>

Christmas tree cataract and myotonic dystrophy type 1

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Received: 14 March 2018 / Revised: 2 May 2018 / Accepted: 1 June 2018 / Published online: 9 July 2018
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We have read with great interest the recent article by Papadopoulos et al. [1] reporting early onset posterior subcapsular cataract in 9 out of 28 patients with myotonic dystrophy type 2 (DM2). They also mentioned that this type of cataract was the first symptom in 7 (25%) of the studied DM2 patients.

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Acknowledgements We thanked Dr. Peter Good/Dr. Emma Berrow with their visual function team and Ms. Rosie Auld with her orthoptic team for their accommodative prompt services in performing/interpreting the results of visual function tests at various stages.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Here, we would like to present our results regarding the incidence of Christmas tree cataract in patients with the most common form of DM, myotonic dystrophy type 1 (DM1). Christmas tree cataract is considered a characteristic finding in subjects with DM1. The retrospective review of medical records of 23 patients with DM1 revealed the presence of Christmas tree cataract in 13 patients (56%). The multicoloured, iridescent lens opacities were unilateral in 10 out of the 13 patients and asymmetric bilateral in 3 patients. Age when cataract was diagnosed was 47 ± 5 years (range: 35–52 years). The cataract was the first sign of the disease for 11 patients and was detected accidentally during a routine ophthalmological examination. Best corrected visual acuity was 0.06 ± 0.08 logMAR (range: -0.1 to 0.2 logMAR). The interval between diagnosis of cataract and DM1 was 10 ± 2 years (range:

7–14 years). This delay is explained by the fact that none of the patients presented typical symptoms of DM1 at the time of the diagnosis of the cataract. Remarkably, apart from Christmas tree cataract, no other form of cataract was detected in the study group, as well as no other pathology regarding the anterior or posterior segment was recorded.

Notably, in previous studies, Christmas tree cataract has been detected in nearly all patients with DM1, and viceversa 16.7% of subjects with Christmas tree cataract have been diagnosed with DM1 [2].

In conclusion, earlier detection of Christmas tree cataract, which constitutes a common ophthalmologic finding in DM1 patients [3, 4], and thus, referral for neuromuscular assessment could possibly eliminate delays in diagnosis of the disease. Noteworthy, it seems that Christmas cataract may be the first manifestation of DM1 in a higher percentage of patients than posterior subcapsular cataract in DM2 patients. Extended multicenter studies may elucidate the exact incidence of the different cataract types in these patients.

Eye (2018) 32:1795–1796
<https://doi.org/10.1038/s41433-018-0171-7>

Hypothyroidism and non-infectious uveitis

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Received: 7 February 2018 / Accepted: 12 February 2018 / Published online: 24 July 2018
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Understanding the non-specific symptoms of uveitis and its corroboration with systemic findings may give insight into its pathophysiology and may in turn help in its management. Association of thyroid disorders with uveitis is well known; however, emphasis has not been made in most of the past studies regarding its prevalence and spectrum of presentation [1, 2].

We performed a prospective analysis of patients presenting at our uvea clinic at a tertiary eye care center in Northern India and evaluated the patterns of uveitis in our

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all patients and the study was approved by the institutional review board at the University of Patras.

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population. As a part of study we also analyzed the prevalence of associated systemic diseases and systemic symptoms. We observed that 24.5% of patients of uveitis had underlying systemic disease, where past or present evidence of tuberculosis was most common followed by seronegative spondyloarthritis and sarcoidosis with overall prevalence of 6.8%, 4.1%, and 2.5%, respectively. Prevalence of hypothyroidism in these patients was 1.5% amongst (12 patients out of 800) all patients and 6.1% among patients with known systemic illness. There were 10 females and 2 males with median age of 37 years (Table 1). Spectrum of involvement was varied, with intermediate uveitis (IU) being the most common presentation. All patients had confirmed hypothyroidism and were on thyroid replacement therapy. None of them suffered from hyperthyroidism. Thyroid functions tests and anti-thyroid

Table 1 Demographic features, laterality and anatomical involvement in patients with thyroid dysfunction and uveitis

Age of patient (years)	Gender	Laterality of the disease	Anatomical classification of uveitis	Systemic symptoms
20	Male	Unilateral	Posterior	Joint pains
40	Female	Bilateral	Intermediate	None
33	Female	Unilateral	Intermediate	None
32	Female	Bilateral	Anterior	None
35	Female	Bilateral	Anterior	None
36	Male	Unilateral	Intermediate	None
38	Female	Bilateral	Panuveitis	None
52	Female	Bilateral	Anterior	None
40	Female	Unilateral	Intermediate	None
42	Female	Bilateral	Intermediate	None
42	Female	Unilateral	Intermediate	Joint pains
33	Female	Unilateral	Anterior	None

antibodies were not ordered at the time of presentation as all patients were already on treatment.

Numerous studies have described systemic associations of uveitis, however, only a few studies have reported such an association between thyroid dysfunction and uveitis [3, 4]. Also, none of them have assessed the prevalence and type of uveitis. A previous study that investigated the relationship between thyroid dysfunction and uveitis, concluded that hypothyroidism was a more frequent association [1]. Our analysis echoed similar results with none of the patients having hyperthyroidism. However, aforementioned study tested thyroxine levels in all patients with or without a specific etiological diagnosis whereas our study included only patients with an established diagnosis of hypothyroidism by an endocrinologist. When compared to prevalence of hypothyroidism in community, nearly 10% of normal population also have subclinical hypothyroidism [5]. Hence, the data described here might be an underestimation of associated hypothyroidism because we did not

order thyroid function tests in other idiopathic uveitis which is a major limitation.

Another important component of our analysis was the anatomical category of uveitis. This revealed IU as being the most common presentation (50%). Similar study evaluating systemic associations in IU, showed an overall prevalence of thyroid dysfunction at 6.02% among all patients of IU and 19.23% amongst patients with known systemic illness [2]. In their study 3 patients had hypothyroidism. Although we cannot decipher a direct causal relationship of thyroid abnormalities and uveitis, concurrent systemic disease may play a role in predisposition for the same.

In conclusion, we highlight surprisingly frequent prevalence of thyroid dysfunction in patients with non-infectious uveitis and its varied presentations. Routine evaluation of thyroid function and related antibodies in cases of idiopathic uveitis may likely seem justified and may reveal a higher association.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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