CASE REPORT

Use of multiple immunosuppressive agents in recalcitrant *ACANTHAMOEBA* scleritis

Eстера Igras, Conor Murphy

Ophthalmology Department,
Royal Victoria Eye and Ear
Hospital, Dublin, Ireland

Correspondence to
Dr Eстера Igras, estera_igras@hotmail.com

Accepted 27 March 2015

SUMMARY

A 48-year-old woman who is a contact lens wearer presented with unilateral *ACANTHAMOEBA* keratitis, confirmed by PCR, which responded initially to topical polyhexamethylene biguanide (PHMB) and bromolene. Three months later, despite continued treatment, she developed diffuse anterior scleritis with severe pain and marked scleral injection but without evidence of recurrence keratitis. Oral non-steroidal anti-inflammatories and oral high-dose corticosteroids were added without success. Subsequent treatment with intravenous methylprednisolone and high-dose cyclosporine led to a temporary improvement. Re-presenting with signs of recurrent scleritis and severe pain, the antitumor necrosis factor monoclonal antibody adalimumab, and later oral cyclophosphamide, were added. This led to complete quiescence of the scleritis. Unfortunately, frequent recurrences of *ACANTHAMOEBA* keratitis and anterior uveitis occurred on immunosuppression requiring continued treatment with PHMB, bromolene and topical corticosteroids. This is the first case of severe refractory *ACANTHAMOEBA* scleritis requiring the concomitant use of four immunosuppressive agents to achieve continued disease control. The challenges in managing this case are discussed.

BACKGROUND

ACANTHAMOEBA keratitis (AK) is a rare but potentially devastating corneal infection, usually occurring in healthy soft contact lens wearers.¹ *ACANTHAMOEBA* scleritis (AS) is an infrequent but severe complication of AK that presents with severe ocular pain and destruction of scleral tissue.²⁻³ The management of AS is challenging and may require systemic immunosuppression as well as antiprotozoan therapy. To date, all reported cases of AS have been successfully managed with either corticosteroids alone or with the addition of cyclosporine A or azathioprine.⁴⁻⁵ Here we report a case of refractory AS that required multiple immunosuppressive agents, including cyclophosphamide and antitumour-necrosis factor (TNF) therapy, showing the potential use of these agents to achieve disease control.

CASE PRESENTATION

A 48-year-old woman presented with a 2-week history of lacrimation, pain and photophobia in her left eye, treated unsuccessfully by her general practitioner with topical antibiotics and corticosteroids. She was a soft contact lens wearer using daily disposable lenses. Her history was otherwise unremarkable. On presentation, her visual acuity was 6/6 in the

right eye and 6/7.5 in the left using a Snellen chart. The Snellen chart is read at 6 m and has 11 lines of blocked letters that decrease in size from top to bottom; 6/6 is the smallest line that a person with normal acuity can read at 6 m. Examination showed perineural infiltrates in the superior and temporal corneal stroma with diffuse superficial stromal haze in the left eye. A diagnosis of AK was confirmed by PCR on a corneal swab. She responded well to topical treatment with a combination of polyhexamethylene biguanide (PHMB) and propamidine isethionate (Brolene), which was tapered down slowly and continued once daily. Asymptomatic for a further month, she developed increasingly severe left eye pain though acuity remained 6/7.5. Examination revealed globe tenderness and markedly engorged episcleral and scleral vessels. The cornea was normal apart from minimal stromal haze and showed no signs of active keratitis (figure 1A, B).

INVESTIGATIONS

A B-scan ultrasound showed normal posterior scleral thickness.

TREATMENT

A diagnosis of diffuse anterior scleritis secondary to *ACANTHAMOEBA* was made and she was started on oral non-steroidal anti-inflammatory drugs (NSAIDs), followed several days later by oral steroids. Topical anti-*ACANTHAMOEBA* agents were temporarily increased in case the worsening pain was due to a subclinical recurrence of the AK, although there were no clinical signs of active keratitis (figure 1A, B). There was no improvement in her scleritis and she required multiple analgesics, including opiates, to control the pain. Following a 3-day course of intravenous methylprednisolone, she experienced a significant improvement in pain and scleral injection. She was maintained on high-dose prednisolone and cyclosporine A was added. Attempts to reduce the prednisolone caused a reoccurrence in her scleritis (figure 2A). As before, the cornea remained quiet. A repeat course of intravenous methylprednisolone resulted in some improvement but the scleritis remained active causing excruciating pain and scleral tissue thinning. Given this, she was started empirically on the antitumour-necrosis factor monoclonal antibody adalimumab 40 mg subcutaneously every 2 weeks.

Several months later she re-presented with active keratitis necessitating an increase in her PHMB and bromolene eye drops and the initiation of topical prednisolone acetate 0.5%. This led to resolution of the corneal signs but because the scleritis was still very

CrossMark

To cite: Igras E, Murphy C. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208536

Figure 1 (A) The left cornea was quiet and showed minimal anterior stromal haze and a healthy epithelium when the scleritis developed. (B) Marked medial scleral injection in the left eye consistent with diffuse anterior scleritis.

active in spite of prednisolone, cyclosporine and adalimumab, cyclophosphamide 50 mg twice daily orally was started. Though the scleritis slowly responded to this regimen over the following

Figure 2 (A) Severe diffuse anterior scleritis before the start of cyclophosphamide and adalimumab. (B) Quiet left eye after successful treatment with cyclophosphamide and adalimumab in combination with low dose prednisolone and tacrolimus.

month, she developed multiple steroid and cyclosporine-induced side effects including hypertension, proximal myopathy and hirsutism, necessitating a switch to oral tacrolimus and a marked reduction in the prednisolone. Oral antiglycaemic and antihypertensive agents were also required. The scleritis finally became quiescent on the following combination of four immunosuppressive agents: prednisolone, tacrolimus, cyclophosphamide and adalimumab (figure 2B), although the cyclophosphamide was subsequently discontinued because of hepatotoxicity.

OUTCOME AND FOLLOW-UP

Her eye has remained quiet and systemic therapy has been slowly reduced. Attempts to decrease the topical therapy were met with recurrences of anterior uveitis or corneal epithelial breakdown suggestive of recurrent AK, necessitating intermittent increases in her topical therapy. On follow-up, her visual acuity gradually decreased from 6/7.5 to counting fingers, predominantly due to the development of a posterior subcapsular cataract but also due to corneal stromal haze from recurrent episodes of keratitis. Her scleritis has remained well controlled for the past 1 year on a combination tacrolimus, prednisolone and adalimumab, in addition to topical prednisolone, brolene and PHMB.

DISCUSSION

Here we present a patient with recalcitrant AS that needed multiple combined immunosuppressive agents to achieve disease control. AS, while rare, occurs in up to 14% of cases of AK.² This patient presented initially with signs typical of AK including perineural corneal infiltrates with diffuse superficial stromal haze. Other signs of AK include punctate keratopathy, pseudodendrites and epithelial or subepithelial infiltrates.⁶ Early diagnosis of AK is important, as prompt treatment is associated with a better visual prognosis. Laboratory tests used to diagnose *ACANTHAMOEBA* include: direct microscopy examination with Giemsa staining, culture and PCR. Direct examination has poor sensitivity compared with culturing,⁷ though cultures usually take several days. PCR is increasingly used, as its sensitivity is superior.⁸ It is important to combine different tests to increase diagnostic accuracy. Cultures can identify coinfection with endocytobionts that may contribute to the pathogenesis.^{9 10} In this case, culture was not performed and coinfection may have contributed to the complexity of the case. One of the consequences of AK is scleritis. AS is defined as the presence of recent or concurrent ipsilateral AK associated with severe ocular pain and scleral inflammation, manifesting as deep pain with globe tenderness associated with engorgement of episcleral and scleral vessels and destruction of scleral tissue (scleromalacia).⁴ Although, the pathogenesis of AS is poorly understood, there is evidence that the invasion of *ACANTHAMOEBA* into the sclera can result in direct stimulation of the immune system causing active scleritis, explaining the potential usefulness of immunosuppressive drugs.¹¹ Unresponsive AS is uncommon, occurring in approximately 10% of cases. Most reported cases are managed successfully with high-dose NSAIDs and topical steroids.⁴ In a case series of 19 patients with AS, all patients responded well to prednisolone alone or required additional second-line immunosuppressive therapy with cyclosporine or azathioprine.⁴ In our case, multiple immunosuppressives were required to control the scleritis including tacrolimus, cyclophosphamide and the anti-TNF monoclonal antibody adalimumab, in addition to topical, oral and intravenous steroids as well as topical antiacanthamoeba therapy.

To the best of our knowledge, this is the first reported case of AS describing the use of cyclophosphamide or anti-TNF

Learning points

- ▶ *ACANTHAMOEBA* is a rare but potentially devastating ocular infection, usually occurring in healthy soft contact lens wearers.
- ▶ *ACANTHAMOEBA* scleritis (AS) is an infrequent but severe complication of *ACANTHAMOEBA* keratitis that presents with severe ocular pain and destruction of scleral tissue (scleromalacia).
- ▶ The management of AS may require multiple systemic immunosuppressive agents as well as antiprotozoan therapy to control ocular inflammation.
- ▶ Adverse drug effects can occur with high-dose and combination immunosuppression including hypertension, glucose intolerance, proximal myopathy and hirsutism.
- ▶ We report the first case of AS requiring the use of multiple systemic immunosuppressive agents including cyclophosphamide and antitumour-necrosis factor therapy.

therapy. This case also highlights some of the many adverse effects that can occur with high-dose and combination immunosuppression. Although our patient developed multiple systemic side effects, all of these were managed by either drug dose reduction or the introduction of additional therapies. The patient's dependence on topical anti*ACANTHAMOEBA* and corticosteroid therapy and the frequency of recurrences of keratitis may also represent an adverse drug effect as the host immune response, necessary to clear active trophozoites from the cornea, was so effectively suppressed.

In summary, we report our experience in managing recurrent AK associated with severe recalcitrant AS. This case also

highlights the potential dangers of combination immunosuppressive therapies.

Contributors CM provided ophthalmic care to the patient and contributed to writing the manuscript. EI drafted the manuscript and also contributed to the care of the patient. All the authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Radford CF, Bacon AS, Dart JK, *et al.* Risk factors for acanthamoeba keratitis in contact lens users: a case-control study. *BMJ* 1995;310:1567–70.
- 2 Mannis MJ, Tamaru R, Roth AM, *et al.* Acanthamoeba sclerokeratitis. Determining diagnostic criteria. *Arch Ophthalmol* 1986;104:1313–17.
- 3 Dougherty PJ, Binder PS, Mondino BJ, *et al.* Acanthamoeba sclerokeratitis. *Am J Ophthalmol* 1994;117:475–9.
- 4 Lee GA, Gray TB, Dart JK, *et al.* Acanthamoeba sclerokeratitis; treatment with systemic immunosuppression. *Ophthalmology* 2002;109:1178–82.
- 5 Pineda R II, Kocaturk T, Bhui RD. Visual outcome and rehabilitation in a case of bilateral acanthamoeba sclerokeratitis. *Cornea* 2007;26:1150–2.
- 6 Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. *Am J Ophthalmol* 2009;148:487–99.
- 7 Khairnara K, Tambera GS, Ralevska F, *et al.* Comparison of molecular diagnostic methods for the detection of Acanthamoeba spp. from clinical specimens submitted for keratitis. *Diagn Microbiol Infect Dis* 2011;70:499–506.
- 8 Boggild AK, Martin DS, Lee TY, *et al.* Laboratory diagnosis of amoebic keratitis: comparison of four diagnostic methods for different types of clinical specimens. *J Clin Microbiol* 2009;47:1314–18.
- 9 Scheid P, Zöller L, Pressmar S, *et al.* An extraordinary endocytobiont in Acanthamoeba sp. isolated from a patient with keratitis. *Parasitol Res* 2008;102:945–50.
- 10 Scheid P. Relevance of free-living amoebae as hosts for phylogenetically diverse microorganisms. *Parasitol Res* 2014;113:2407–14.
- 11 Ebrahimi KB, Green WR, Grebe R, *et al.* Acanthamoeba sclerokeratitis. *Graefes Arch Clin Exp Ophthalmol* 2009;247:283–6.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow