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EDITORIAL

The evil curse of ocular pemphigoid

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Ocular mucous membrane pemphigoid (OcMMP) is a serious conjunctival disorder that remains problematic for many clinical reasons. Those familiar with the condition will know that the patient's difficulties start right from the day of presentation and continue throughout life. Some term it as the 'conjunctival curse' as patients are often consigned to life-long ocular and systemic misery.

For those who are not familiar with OcMMP, the disease may affect only the conjunctiva (ocular pemphigoid) with systemic mucous membrane involvement (mucous membrane pemphigoid). The ophthalmic clinical picture can be quite variable, starting with recurrent conjunctivitis, episodes of conjunctival hyperaemia, and mucous discharge. In more acute stages, patients can develop conjunctival vesicles that burst, resulting in conjunctival ulceration. As the condition progresses, the conjunctivae undergo considerable shrinkage and fibrosis; leading to symblepharon, ankyloblepharon, xerophthalmia, keratoconjunctivitis sicca, entropion, and trichiasis formation. These result in ocular surface disfigurement with huge corneal compromise, resulting in corneal ulceration, infection, and ultimately blindness.[1]

The challenges for clinicians are as follows: how do you make a diagnosis, especially in the early stages? What is the likely clinical course in a particular patient? What defines active disease? What treatment options should be chosen at each stage of the condition? Can, if ever, immunosuppressive therapy be stopped?

The initial challenge is with diagnostic confusion and appropriate recognition. The problem at this stage is, except for more advance disease, a chronic conjunctivitis can be confused with infective aetiologies. Unless a biopsy is taken for direct immunofluorescence the condition could be missed.[2] Some centres may use indirect immunofluorescence, which may only be positive 30–40% of the time.[1–3] Thus with a negative biopsy result, the clinician is then left making the diagnosis based on the early clinical course of disease, when features may be confused with other causes.[1] Because of the dilemma of starting immunosuppressive therapy, a clinician would be reluctant to make a diagnosis purely on clinical suspicions.

However, even if the diagnosis is established, the clinical tribulations only intensify. Which immunosuppressive regime should be used? If OcMMP is stable and non-progressive, when can you stop immunosuppression?

Of course, the only way of finding out, is to conduct large longitudinal national studies of the disease. It is welcoming that in this issue Williams *et al*[3] provide a snapshot of what happens to patients with OcMMP in the UK. They show the pattern of referrals in two leading tertiary referral centres. Their study that gives the time period of symptoms before a definitive diagnosis is made. More importantly, they show that OcMMP presents in two broad age groups, in one group there is a younger set of patients that typically have more acute inflamed clinical presentation and the other is an older group that typically has established disease.[3] Interestingly, they found both groups progressed similarly!

A common demographic description is that OcMMP affects significantly more females than males with a ratio of 1.6.[1,4] However, Williams *et al*[3] show that the case distribution is more even with ration closer to 1 : 1. Although there may be limitations in their methodology, such as reporting and selection bias, their study does provide a useful snapshot.

It may be obvious that delays in early diagnosis and management of this condition would lead to delays in receiving appropriate therapy. However, an early diagnosis remains a challenge. Williams *et al* show that the 'gold standard' of histological diagnosis using direct immunofluorescence, showing deposition of immunoglobulins and complement on the conjunctival basement membrane zone is very helpful.[2,3] They show that this is positive in up to 92% early onset patients, however, there remains a significant number of patients who

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have a negative biopsy.[3] This is important as the clinician is presented with the vexed question as to whether to start empirical immunosuppressive therapy with all the medical consequences that entails.

Even if we are confident of the diagnosis or confirmed its presence, we know that with good immunosuppression, there are many patients who have progressive disease. Williams *et al*[3] show that there is a subset of patients that remain either completely refractory to conventional immunosuppression or relapse despite initial success. Williams *et al*[3] emphasise the need for referral to a tertiary centre, where expertise in using 'step-up' therapy can be helpful in halting progressive disease.

It is also interesting that the authors show that 42% demonstrated disease progression in the absence of clinically detectable inflammation. They have used clinical markers such as fornix depth measurer. Currently, there is no standardised method for measuring and documenting disease progression, for example, the upper fornix, when the disease asymmetrically involvement of the superior *vs* the inferior conjunctival surface. The availability of biomarkers of disease progression is important, as these could potentially address the issue of sub-optimal therapeutic immuno-modulation of disease course and directing appropriate therapy.

Clearly further research is required to determine accurate biomarkers that indicate disease progression. Encouragingly, molecular studies have shown altered levels of systemic cytokines, where serum levels of interleukin-1 and TNFα are elevated, and levels of interleukin-1 receptor antagonist and interleukin-6 are decreased in active OcMMP.[5,6] Others have also shown a dysregulation of TGFβ levels in the inflamed conjunctiva with active OcMMP.[7] These observations could be used as an 'activity index' and form the basis for the use of specific targeted biological therapies.[8]

Thus OcMMP remains a challenging disease to manage. Williams *et al*[3] data re-emphasise and strengthen the case for further studies both clinical and laboratory. Greater understanding of disease pathology is required to facilitate earlier consistent recognition of disease, to determine progression, and allow more accurate therapeutic targeting. At the moment, the best option for patients is to be referred to a tertiary centre that uses a 'step-up' approach. Nevertheless, despite prompt and appropriate actions, OcMMP patients are trapped in an awkward fate. That is the evil curse OcMMP!

Conflict of interest

The author declares no conflict of interest.

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