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Use of intravenous cyclophosphamide in the prevention of corneal melt: justified or not?

Sir, We read with interest the article by Clewes et al. about the prophylactic use of intravenous cyclophosphamide in the management of the ocular conditions of two rheumatoid arthritis patients. The authors used the term ‘peripheral ulcerative keratitis’ or PUK in describing the ocular conditions. However, from the clinical information provided, this blinding ocular condition occurred as a complication after ophthalmic surgery [1]. We believe that instead of PUK, the authors were actually reporting cases of surgically induced necrotizing sclerokeratitis (SINS), which is an ocular condition with totally different manifestation, pathogenesis, treatment strategy and prognosis [2–5].

Clinically, PUK refers to a peripheral corneal lesion located in the vicinity of, or straddling across, the cornea–sclera junction, whereas SINS represents a frank scleral inflammation sparing the cornea [2, 3, 5]. SINS usually does not invade the limbus until an advanced stage of disease [2]. Pathogenetically speaking, surgical manipulation or trauma is the sine qua non for the development of SINS as surgical exposure of formerly immune-privileged tissue antigens to the immune system is thought to be the mechanism [2, 3]. Connective tissue disease is not a prerequisite for SINS because only 63% of SINS patients have underlying medical conditions [2]. Moreover, SINS shows no relationship with the activity of the systemic connective tissue disease [2]. Conversely, PUK occurs as a result of vasculitic involvement of the limbal or corneal–scleral junction vessels [5]. This is usually part of the manifestation of underlying systemic vasculitis and may herald a potentially lethal flare-up [5]. Therefore, the onset of PUK in the course of connective tissue disease carries a grave prognosis, not only for the eye but also for general well-being [5]. It necessitates prompt immunosuppressive therapy with corticosteroids and cytotoxic agents in order to save life [5]. On the other hand, concerning the management of SINS, there is an array of treatment plans, including non-steroidal anti-inflammatory agents, immunosuppressive treatment and the local surgical replacement of damaged ocular tissue [2]. Irrespective of the form of therapy, the goal of treatment in SINS, unlike that of PUK, is to control ocular tissue destruction, salvage vision and maintain the integrity of the globe [2].

The interchangeable use of PUK and SINS is extremely unusual and may suffer from the pitfall of inaccuracy. The authors have declared no conflicts of interest.

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Red flags need more evaluation

Sir, The recent review on the role of physiotherapy in the management of non-specific back pain and neck pain [1] failed to highlight a large deficit in the evidence-base of low back pain management. Whilst the review draws upon high-quality evidence to make recommendations for treatment, this was not the case when recommendations were made on the use of ‘red flags’ to screen for serious pathology. Practitioners were encouraged to use the list of red flags provided in Table 1 to screen for serious pathology. Readers were advised that if any red flag is found, a prompt referral to a specialist for further investigation needs to be arranged. However, readers should be advised against uncritical acceptance of this recommendation.

It seems to have gone largely unnoticed that there is little or no high-quality evidence on the diagnostic accuracy of red flags and that on the limited evidence available, some red flags seem to have little diagnostic power. In our view, this situation has probably arisen because the guidelines that have promoted the red flags (e.g. the recent European Guidelines [2]) have relied upon secondary citation [3] or referred to studies [4] which did not seek to assess the diagnostic accuracy of the features. The dangers of secondary referencing are well-known and are particularly evident here, with perhaps the most important part of the clinical examination becoming orthodoxy without any supporting data. As an example, Moffett and McLean’s review [1] and many other guidelines promote thoracic pain as a red flag; however, the only study that evaluated this clinical feature reported a positive likelihood ratio of 1.1 and a negative likelihood ratio of 1.0, indicating that this feature has no value in screening for serious spinal pathology [5].

Leaving aside the uncertainty about the diagnostic accuracy of red flags, Moffett and McLean’s [1] suggested approach to diagnostic triage may not be feasible in many health care settings. Moffett and McLean [1] advocate that if any of the 12 red flags in Table 1 are present the patient should be referred to a specialist. Deyo and Diehl [5] showed that requiring any of the four red flags to be positive (age >50, or a history of cancer, or unexplained weight loss, or failure of conservative therapy) detected all cases of cancer; however, there was a false alarm rate of 40%. Based upon
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Deyo and Diehl's [5] data, Moffett and McLean's [1] strategy is likely to detect all cases of cancer; however, it will have an even higher high false alarm rate and so will probably create unmanageable workloads for specialists. A better strategy for primary care may be that described by Jarvik and Deyo [6], where if any red flags are positive plain radiographs and simple blood tests such as erythrocyte sedimentation rate (ESR) are first ordered as an intermediate step before considering the need for more advanced imaging or specialist review.

In our view, the current body of low back pain research is unbalanced because there has been too little research evaluating the accuracy of the red flags. For example, while there are 564 clinical trials of physiotherapy treatments for low back pain [7], there are only a handful of studies that have evaluated screening for cancer with red flags. Without high quality data on the accuracy of the red flag questions, recommendations on their use in routine clinical practice cannot be confidently made. Further high quality studies in primary care settings are obviously needed as the accuracy of the diagnostic tests used in physiotherapy is as important as data regarding the effectiveness of management strategies.

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Re: Use of intravenous cyclophosphamide in the prevention of peripheral ulcerative keratitis

SIR, Liu and Chan are confused in their assumptions. In our report, we described two patients with rheumatoid arthritis, who had previous peripheral ulcerative keratitis (PUK) leading to the perforation of the eye [1]. We discuss the repeated use of cyclophosphamide to prevent recurrence of the vasculitis manifesting as a PUK. The development of PUK following previous surgery is well-recognized [2]. Sainz de la Mata et al. [2] found that patients with peripheral keratopathy were 4.8 times more likely to have had previous ocular surgery. In particular, they noted that PUK was significantly associated with previous ocular surgery in 58.3%, and was the most frequent peripheral keratopathy found after cataract surgery [2]. Vasocclusive changes are prominent in the episclera adjacent to the site of the PUK [3], and histologically there is an inflammatory micro-angiopathy of the episcleral and conjunctival vasculature [4].

In contrast, surgically induced necrotizing sclerokeratitis may be associated and precipitated by a variety of conditions such as a localized infection or inflammation around a suture, and may not be associated with a systemic connective tissue disorder. The two patients we have reported had an underlying connective tissue disorder with an evidence of a previous vasculitis. As has been