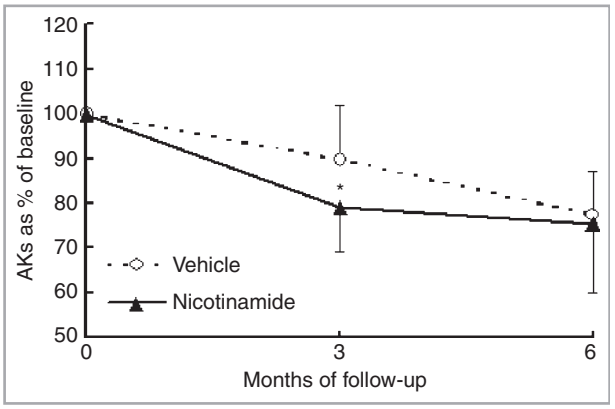

Fig 1. Actinic keratoses (AKs) were counted at baseline, 3 months ($n = 30/30$) and 6 months ($n = 28/30$) in patients randomized to apply either 1% nicotinamide or vehicle gel twice daily to affected sites (i.e. whole face, scalp, hands and forearms as appropriate).

In our elderly population, with numerous baseline AKs, nicotinamide-treated patients had a significant 22% reduction in AKs at 3 months, compared with a nonsignificant 10% reduction with vehicle. This treatment difference was not maintained at 6 months. The 22% reduction in vehicle-treated AKs at 6 months is consistent with other studies,[8] confirming that AKs often spontaneously resolve. Nicotinamide may have accelerated the natural seasonal resolution of AKs, possibly by reducing UV immunosuppression.[5] We used 1% nicotinamide here, and while a higher concentration or different formulation may have increased efficacy, previous studies found similar immunoprotection with 5% compared with 0·2% nicotinamide.[2,5]

Our patients were sun damaged with multiple prior skin cancers, living with high year-round UV. Sunscreen use was surprisingly low, with only 17% always wearing sunscreen outdoors, and a third confessing to never using sunscreen. Daily use of sunscreen has previously been shown to reduce AK numbers by ~40%,[9] and greater immunoprotection would likely be achieved with nicotinamide plus sunscreen rather than with nicotinamide as a sole intervention. Previously, we found greater susceptibility to UV immunosuppression in men than women,[5] consistent with findings in male mice.[10] In the present study, the trend towards greater nicotinamide efficacy in men could reflect their greater potential for immune protection.

Our study was designed as a pilot to rapidly assess the potential for a safe, inexpensive intervention to reduce AKs. We found a more rapid rate of AK resolution with nicotinamide compared with vehicle in a group of heavily sun-damaged individuals. Future, larger studies using nicotinamide at higher concentrations, or with concurrent sunscreen are now warranted.

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Key words: *niacinamide, precancers, skin cancer, ultraviolet immunosuppression*

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Radiotherapy: a protective role for toxic epidermal necrolysis?

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Madam, Toxic epidermal necrolysis (TEN) is a rare but serious dermatological disease with significant morbidity and mortality. The condition was first described by Lyell approximately 60 years ago and is characterized by extensive epidermal death. While drugs are well-known triggers, there are reports of TEN and Stevens–Johnson syndrome (SJS) developing after receiving radiotherapy (RT) concomitantly with medication.[1]

We present a case of TEN where RT appears to have had a protective role.

A 49-year-old man with a history of metastatic rhabdomyosarcoma was admitted with pneumonia and treated with intravenous co-amoxiclav (Augmentin®; GlaxoSmithKline, Uxbridge, U.K.) and levofloxacin (Tavanic®; Hoechst Marion Roussel, Guildford, U.K.) for 5 days. A week later he developed a tender, erythematous eruption in his groins and lower abdomen which evolved over the next 48 h into erythroderma and extensive blistering, affecting approximately 60% of his body surface area. A sharply demarcated rectangular area of skin on his chest, mirrored on his back, appeared to be entirely unaffected (Fig. 1a,b). This was the site of RT which he had completed 3 months previously for superior vena cava obstruction from pulmonary metastases. The RT treatment he received at that time was uneventful. Importantly, there had been no application of topical medications, such as steroids, to the chest and back prior to, during, or post-RT.

Laboratory investigations showed a normal white blood cell count with lymphopenia, anaemia, significantly raised inflammatory markers, low albumin, reduced bicarbonate level but normal urea and glucose. While skin swabs were negative, blood cultures were positive for enterococci and coagulase-negative staphylococci. A diagnostic biopsy revealed a subepidermal split with full-thickness epidermal necrosis.

The patient was resuscitated, all nonessential drugs were discontinued and he was treated with intravenous immunoglobulin (Vigam®; Bio Products Laboratory, Elstree, U.K.) 1 g kg^{-1} daily for 5 days together with intravenous meropenem (Meronem®; AstraZeneca, Luton, U.K.) and vancomycin (Vancocin®; Flynn Pharma, Hitchin, U.K.). Initially, he was managed on the burns unit but subsequently required intensive care support. Our patient made an excellent recovery and was able to return home 8 days later. As his skin returned to normal, the rectangular areas on his chest and back were no longer visible.

The annual incidence of TEN is 1–2 per million of population. In the majority of cases there is a history of drug ingestion. While numerous treatment modalities have been employed, the evidence appears to be conflicting in terms of their efficacy. These include corticosteroids, ciclosporin, cyclophosphamide, intravenous immunoglobulin, plasmapheresis, insulin, zinc, and granulocyte colony-stimulating factor.[2] Currently the evidence is, therefore, not sufficiently strong to suggest a definitive single treatment. A combined approach appears indicated including drug elimination, immunosuppression and aggressive supportive care, preferably delivered on a specialist intensive care or burns unit. Multidisciplinary teamwork is crucial to optimize the chances of a favourable outcome.

The pathogenesis of TEN is both complex and conflicting. Our understanding of the apoptotic pathways in keratinocytes and lymphocytes together with the specific immunological changes related to drug reactions offers valuable insights. In TEN, the drug appears to induce an HLA class I-restricted, specific drug sensitivity, resulting in clonal expansion of CD8+ cytotoxic T lymphocytes (CTLs), with the key cytokine being interleukin 2. Cytotoxicity is mediated by CTL granzyme and possibly death receptor (DR) ligand and probably increased expression of Fas ligand on the keratinocyte.[3] Tumour necrosis factor (TNF) may well also contribute via the TNF receptor 1 death pathway.[4] Keratinocyte apoptosis may therefore occur by a two-step process: firstly, a CTL-driven process (as occurs in other drug reactions), and secondly, an amplification mode specific to TEN, dependent on upregulation of DR ligand.

RT is a recognized important therapeutic option in treating a wide range of malignancies, and the resultant cutaneous side-effects are well known. During or after RT, approximately 5% of cancer patients develop either an acute radiotoxic response such as erythema and desquamation, or late adverse reactions, such as fibrosis and telangiectasia.[5] There is good evidence suggesting a genetic basis for the predisposition to side-effects of RT in healthy tissue.[6] Thus, dysfunction of genes and their protein products involved in the recognition and processing of the cellular radiation damage could be a possible molecular basis underlying the adverse cutaneous radiotoxic reaction.

Although there are reports of RT being a potential risk factor for developing TEN,[7] to our knowledge this is the first

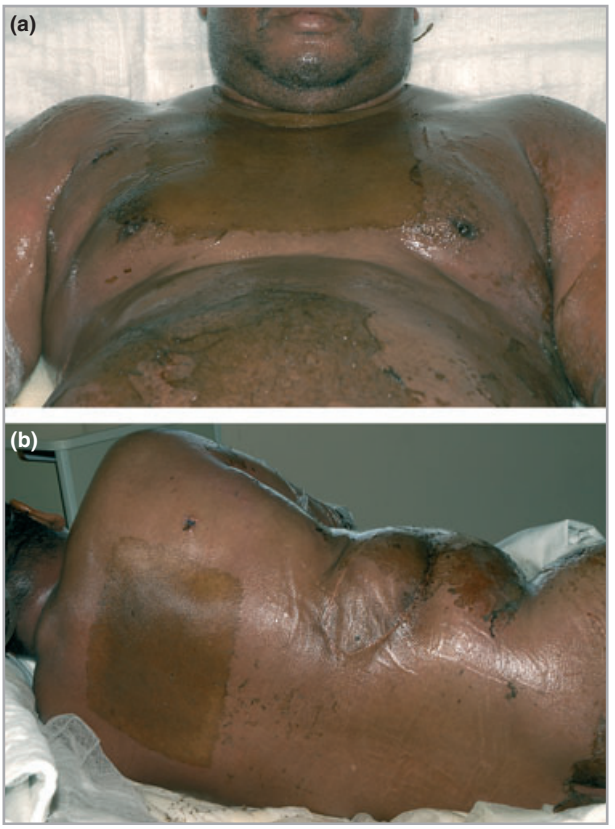

Fig 1. Clinical appearance of the patient, showing apparently unaffected areas of skin on the chest (a) and back (b).

case where RT appears to have had a protective role. We hypothesize that RT may afford protection by inactivation of CTLs, key players in the aetiology of TEN. Interestingly, while the head, neck and thorax regions are usually most prone to radiation damage,[8] in our case this was the only site that was unaffected. Furthermore, a recent study found that black people receiving RT experienced more severe adverse cutaneous reactions compared with their white-skinned counterparts,[9] which is not apparent in this case.

The pharmacogenetic profile of the SJS/TEN spectrum of disorders is both interesting and evolving. The disease appears to be ethnically and drug restricted, with some studies showing associations between HLA-B*1502 allele and carbamazepine-induced SJS in Han Chinese subjects.[10] We therefore speculate that RT may have the opposite effect in different individuals of varying ethnicities. While much more is known about this condition today, more work needs to be done in developing specific targeted therapy in the hope of preventing the consequences of this rare, devastating condition.

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A 'D.I.Y.' nasal plug with airway: an alternative approach

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MADAM, We read with great interest the recent article by Flohr *et al.*[1] describing the use of Merocel® nasal packing with airway as a means of maximizing the contact of skin grafts to the wound bed postoperatively on the nasal tip and ala. The authors are in our opinion, absolutely correct in their assertion that the use of a dental roll for nasal packing is uncomfortable for patients by virtue of the fact that airflow into the nostril is restricted. In an endeavour to make the experience of 'nasal packing' as comfortable as possible for our patients, we have for some time been creating our own version of a 'nasal plug with an airway' using materials readily available and generally present on the surgical tray.

Our technique is illustrated in Figure 1. Local anaesthetic is routinely administered to our patients via a 30-gauge needle (Fig. 1a). If surgery involves the nasal tip and/or ala, the sterile needle cap is kept on the theatre tray, bathing in antiseptic surgical solution for later use.

To assemble the plug, a piece of gauze is wrapped round the cap (up to three times according to the desired diameter required to ensure a secure fit within the nostril) and secured using sterile adhesive tape (Fig. 1b, c). Care is taken to ensure that the end of the cap to be inserted furthest up the nasal vestibule is adequately covered with gauze but also ensuring that the aperture of the cap is not covered. To prevent drying out of the plug, and to increase patient comfort and facilitate its removal at the desired time, paraffin-impregnated gauze is wrapped around the plug (Fig. 1d). The plug is then trimmed to the desired length (Fig. 1e) and in this way the needle cap forms a robust patent airway at the centre of the created plug. For grafts on the ala, we routinely employ the use of a bolster; the plug is thus secured into place with a suture sling or, alternatively as described by