Minimal, superficial DNA damage in human skin from filtered far-ultraviolet C


Published in: British Journal of Dermatology

DOI: 10.1111/bjd.19816

Publication date: 2021

Licence: CC BY

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA):
To find a pathogenetic pathway that could serve as a treatment target, we conducted next-generation sequencing on formalin-fixed tumour. The test identified the NRAS p.Gln61Arg mutation with a variant frequency of 8%.

Due to the failure of previous treatments and the major potential risk of a surgical procedure, we offered the patient an off-label compassionate treatment with trametinib, a mitogen-activated protein kinase kinase (MEK) inhibitor. Following the patient’s consent, treatment was initiated at a dose of 2 mg once daily. The skin lesions were already reduced 1 week after treatment initiation and regression was almost complete after 3 months of treatment, with only a subtle remnant in the upper eyelid (Figure 1d).

Follow-up evaluation included blood pressure measurement, complete blood count, liver and renal function tests, lipid profile, electrocardiography, echocardiogram and ophthalmological examination. The adverse effects included acneiform rash, mild paronychia and asthenia. No severe adverse events were noted.

Recent seminal discoveries have uncovered the role of hyperactivation of the RAS–mitogen-activated protein kinase–extracellular signal-regulated kinase pathway in most vascular anomalies.1,2 PGs harbour mutations in RAS genes. In previous studies six specimens out of 42 sporadic PGs showed mutations in KRAS, NRAS or HRAS,3 and four and one specimens out of 25 PGs arising on port-wine stains showed mutations in BRAF and KRAS, respectively.4

The differential diagnosis in our case was eruptive disseminated PG. PGs are usually solitary, but multiple lesions (satellites) can occur after initial surgical removal5 or following a burn.6 Multiple localized PG-like lesions are termed agminated PGs7 and may follow an aggressive clinical course. Our case showed a focally superficial component with lobular architecture on pathology and clinical behaviour simulating agminated PG. PGs harbour mutations in RAS genes. In previous studies six specimens out of 42 sporadic PGs showed mutations in KRAS, NRAS or HRAS,3 and four and one specimens out of 25 PGs arising on port-wine stains showed mutations in BRAF and KRAS, respectively.4

The differential diagnosis in our case was eruptive disseminated PG. PGs are usually solitary, but multiple lesions (satellites) can occur after initial surgical removal5 or following a burn.6 Multiple localized PG-like lesions are termed agminated PGs7 and may follow an aggressive clinical course. Our case showed a focally superficial component with lobular architecture on pathology and clinical behaviour simulating agminated PG, in association with diffuse acquired unspecified capillary haemangioma, a unique pattern previously unreported.

NRAS is one of the three major isoforms of the RAS family of GTPase proteins. Almost 60% of NRAS tumours harbour mutations at codon 61, and 35% at codon 12.8

In summary, we report a unique case of reactive aggressive vascular proliferation simulating agminated PG with NRAS mutation, and its excellent response to a MEK inhibitor. Our results highlight the potential of targeted therapies in the context of vascular lesions.

S. Greenberger1,2, R. Stein2,3 A. Ollech1,2 M.E. Hartstein2,3 O. Benyamini3 M. Yalon2,4 A. Levi2,5 M. Lapidoth2,5 and A. Barzilai2,6

1Pediatric Dermatology Service, Department of Dermatology, Sheba Medical Center, Ramat-Gan, Israel; 2Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, 69978, Israel; 3Division of Ophthalmic Plastic and Reconstructive Surgery, Department of Ophthalmology and Visual Sciences, Yitzhak Shamir Medical Center, Tel Aviv University, Tiratrim, Israel; 4Pediatric Neuro-Oncoology Service, Pediatric Hemato-Oncoology Department, Chaim Sheba Medical Center, Tel Hashomer, 52621, Israel; 5Department of Dermatology, Laser Unit, Rabin Medical Center, Petach Tikva, Israel; and 6Department of Dermatology, Sheba Medical Center, Ramat-Gan, Israel

Email: shoobane.greenberger@sheba.health.gov.il

References

Funding sources: none.

Conflicts of interest: The authors declare they have no conflicts of interest.

Minimal, superficial DNA damage in human skin from filtered far-ultraviolet C

DOI: 10.1111/bjd.19816

Dear Editor, Krypton chloride (KrCl) excimer lamps have a peak emission wavelength of 222 nm, in the ultraviolet (UV) C region of the electromagnetic spectrum. Currently KrCl lamps are the only viable ‘far-UVC’ sources for full-room inactivation of airborne SARS-CoV-2, the virus responsible for the COVID-19 pandemic.1 Commercially available KrCl excimer lamps can be retrofitted to existing room lamp fittings or mounted at ceiling height independently. Other technologies, such as light-emitting diodes, are currently neither efficient nor powerful enough for such a task.

In addition to the peak KrCl excimer emission wavelength of 222 nm (83% at 200–230 nm), the lamp spectrum contains longer-wavelength UVC (10% at 230–280 nm), UVB (3%) and UVA radiation (4%). These additional wavelengths have been shown in vivo and in silico to penetrate to the skin’s...
basal layer and cause DNA damage.2,3 When the excimer lamp was filtered, reducing these longer wavelengths of UV radiation, a study in 20 healthy volunteers did not show erythema induction 24 h after exposure to 500 mJ cm \(^{-2}\). In that study there was a slight, statistically significant, increase in cyclobutane pyrimidine dimers (CPDs) compared with nonirradiated skin, although the location of the CPDs was not determined. However, computer modelling and animal experiments suggest that these CPDs will be limited in number and restricted to the uppermost parts of the epidermis.2,5 The location of CPDs is important as, if limited to the superficial suprabasal nonproliferating skin cells, it is unlikely that this will indicate a carcinogenic risk. To our knowledge, the location of CPDs from filtered far-UVC radiation, as described above, has never been demonstrated in human skin.

We performed human skin irradiation in two settings using a filtered KrCl far-UVC source (SafeZoneUVC, Ushio Inc., Tokyo, Japan): firstly, in a novel \(\text{ex vivo}\) full-thickness human skin model cultured at tension (manuscript in preparation) and secondly, using in vivo self-exposures. \(\text{Ex vivo}\) human skin was obtained from an abdominoplasty after full consent was obtained. This skin was cultured at the air–liquid interface in RM + medium containing 50 \(\mu\)g mL\(^{-1}\) gentamicin, 200 U mL\(^{-1}\) penicillin, 200 \(\mu\)g mL\(^{-1}\) streptomycin and 0.25 \(\mu\)g mL\(^{-1}\) amphotericin B. There were three samples: an unirradiated negative control sample, a positive control sample irradiated for 188 s delivering a radiant exposure of 515 mJ cm\(^{-2}\); narrowband UVB (peak emission wavelength 311 nm, TL01; Philips, Eindhoven, the Netherlands) and the test sample irradiated for 1000 s delivering a radiant exposure of 6100 mJ cm\(^{-2}\) filtered far-UVC. The human skin provider, Biopredic International, holds permit AC-2013-1754 granted by the French Ministry of Higher Education and Research for the acquisition, transformation, sales and export of human biological material for research.

In vivo, two of the authors irradiated their inner forearms at a dose of 6100 mJ cm\(^{-2}\) of filtered far-UVC, using the same irradiation source and distance as the \(\text{ex vivo}\) samples. Ethical approval was not required for self-exposures in the two senior investigators who led the in vivo aspects of this work.

Punch biopsies (4 mm) were taken from irradiated sites within 30 min of exposure and from nonirradiated sites, and were fixed in freshly prepared 4% paraformaldehyde at 20°C prior to paraffin embedding. CPD abundance was revealed by immunohistochemical staining with monoclonal anti-thymine dimer antibody (T1192; Sigma-Aldrich, St Louis, MO, USA).

Figure 1 displays histological staining of both the \(\text{ex vivo}\) and irradiated \(\text{in vivo}\) skin. As would be expected, there is CPD formation throughout the epidermis following narrowband UVB irradiation in the \(\text{ex vivo}\) skin model (Figure 1b) and no CPDs in the \(\text{ex vivo}\) control sample (Figure 1a). Both the \(\text{ex vivo}\) and \(\text{in vivo}\) filtered far-UVC-irradiated human skin samples show minimal CPD formation (Figure 1c and d, respectively). Where CPD-positive cells were present in one volunteer, importantly they were restricted to the upper layers of the epidermis, with no basal-layer CPD formation detected. Fewer CPD-positive cells were detected in the filtered far-UVC-irradiated skin of the second volunteer, where a thicker stratum corneum was evident, and both control in vivo samples were CPD negative (data not shown).

This first-in-human demonstration of CPD location from filtered far-UVC confirms the results of our previous in silico model and indicates that the peak KrCl excimer emission wavelength of 222 nm does not penetrate beyond the most superficial epidermal layers. The \(\text{ex vivo}\) skin model was also in agreement with the \(\text{in vivo}\) exposures, enabling us to undertake future investigations that would be difficult to perform in humans. The radiant exposure delivered in these experiments

---

Figure 1 Histological staining. (a) Nonirradiated \(\text{ex vivo}\) skin sample. (b) Narrowband ultraviolet (UV)B-irradiated \(\text{ex vivo}\) skin sample. (c) Far-UVC-irradiated \(\text{ex vivo}\) skin sample. (d) Far-UVC-irradiated \(\text{in vivo}\) human skin sample. Formalin-fixed paraffin-embedded skin samples were stained for cyclobutane pyrimidine dimer (CPD) formation using immunohistochemical methods. Arrows are used to highlight examples of CPD-positive cells.
is 265 times the current exposure limit value of 23 mJ cm$^{-2}$ at 222 nm. Therefore, even at very high exposure doses, appropriately filtered far-UVC is unlikely to present a carcinogenic risk through direct DNA damage. These important but preliminary results are very encouraging. As recently advised and encouraged by the UK’s Scientific Advisory Group for Emergencies we are continuing with multiple far-UVC research projects to investigate the efficacy and safety profile of this very promising technology. However, to date, the evidence is overwhelmingly in favour of using filtered far-UVC as a safe, effective germicidal technology.

Acknowledgments: We would like to thank Tatsushi Igarashi and Ushio Inc. for loan of the filtered far-UVC source, SafeZoneUVC.

R.P. Hickerson,1 M.J. Conneely,1 S.K. Hirata Tsutsumi,1 K. Wood,1 D.N. Jackson2,3, S.H. Ibbotson1,4 and E. Eadie3

1 Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK; 2SUPA, School of Physics & Astronomy, University of St Andrews, St Andrews, KY16 9SS, UK; 3Department of Dermatology, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; 4Scottish Photobiology Service, Photobiology Unit, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; and 5Scottish Photobiology Service, Photobiology Unit, NHS Tayside, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK. Email: r.p.hickerson@dundee.ac.uk

Inducible skin-associated lymphoid tissue (ISALT) in a patient with Schnitzler syndrome who manifested wheals on recurrent localized erythema

DOI: 10.1111/bjd.19808

Dear Editor, Schnitzler syndrome is characterized by a chronic urticarial rash with an intermittent fever, and is considered to be an acquired form of autoinflammatory syndrome because its clinical phenotypes are similar to cryopyrin-associated periodic syndrome with a gain-of-function mutation in NLRP3. Patients with Schnitzler syndrome also exhibit IgM monoclonal gammopathy, and 15–20% of patients eventually develop a lymphoproliferative disorder resembling Waldenström macroglobulinaemia with an MYD88 mutation. At present, the precise pathogenesis of Schnitzler syndrome remains unknown.

Chronic inflammation in the skin triggers the development of tertiary lymphoid structures, and in a mouse model, we proposed the term of inducible skin-associated lymphoid tissue (ISALT) that efficiently activates effector T cells. Subsequently, we showed that some inflammatory skin diseases in humans can also form ISALT structures, i.e. formation of the central B-cell zone in lymphoid follicles, lined with the expression of the B-cell chemoattractant CXCL13, while in the surrounding T-cell zone, peripheral lymph node addressin (PNAd)-positive vessels indicating differentiation towards high endothelial venules (HEVs) were observed. Here, we describe a case of Schnitzler syndrome that exhibited ISALT with a peripheral distribution of IgM-expressing plasma cells.

A 63-year-old woman developed an urticarial rash without pruritus on her left cheek and the right side of her neck (Figure 1a). She reported a periodic fever of over 38°C along with general fatigue. Laboratory findings confirmed leucocytosis [18 440 µL$^{-1}$ (normal range 2700–8500)] with marked neutrophilia (84.4%), elevated C-reactive protein [5.4 mg dl$^{-1}$ (0–0.2)], and IgM [1898 mg dl$^{-1}$ (54–333)]. The patient was diagnosed with Schnitzler syndrome. Bone pain was not apparent. Liver and renal function tests were normal. Somatic mosaicism in NLRP3 and MYD88 was excluded.

References

7 International Commission on Non-Ionizing Radiation Protection. ICNIRP guidelines on limits of exposure to ultraviolet radiation of wavelengths between 180 nm and 400 nm (incoherent optical radiation). Health Phys 2004; 87:171–86.

Funding sources: This study was funded in part by MR/P012248/1 to R.P.H. from the Medical Research Council.

Conflicts of interest: R.P.H. and M.J.C. are founders and directors of Ten Bio Limited, a company focused on the development of human skin explant models.