A report and follow up of a patient with disseminated superficial actinic porokeratosis (DSAP) undergoing novel systemic treatment with palifermin (a keratinocyte growth factor) during chemotherapy
A report and follow up of a patient with disseminated superficial actinic porokeratosis (DSAP) undergoing novel systemic treatment with palifermin (a keratinocyte growth factor) during chemotherapy

Matthew Howard¹ B Pharm (Hons) MBBS (Hons), Anthony Hall²,³ MBBS (Hons) Dip RACOG Grad Dip Ven FRACGP FACD

Affiliations: ¹Department of Medicine, St Vincent’s Hospital, Melbourne, Victoria, Australia, ²Skin and Cancer Foundation (Inc), Carlton, Victoria, Australia, ³School of Medicine, Deakin University, Geelong, Victoria, Australia

Corresponding Author: Matthew Howard, 39 Highland Way, Leopold, Victoria, Australia, Postcode 3224, Email: matthew.david.howard@gmail.com

Abstract
Disseminated superficial actinic porokeratosis (DSAP) is an inherited dermatosis triggered by chronic ultraviolet light exposure. Cosmetic improvement has been noted with topical therapies or laser treatment. Lesions of DSAP are precancerous, having been reported to develop into squamous cell carcinomas (SCCs) or basal cell carcinomas (BCCs) occasionally. We describe a patient with longstanding DSAP who developed a primary CNS lymphoma. Palifermin (a keratinocyte growth factor analogue) was used as an adjuvant in the chemotherapy regimen to minimize the expected adverse effect of mucositis. The treating hematologists had reservations that palifermin may lead to the development of invasive squamous cell carcinomas (SCCs) within our patient’s DSAP plaques owing to its mode of action. Our patient noted marked and

Keywords: disseminated superficial actinic porokeratosis, palifermin, DLBCL, keratinocyte growth factor, DSAP, SCC, BCC

Introduction
This report describes a patient with longstanding disseminated superficial actinic porokeratosis (DSAP) who developed a primary CNS lymphoma. Palifermin (a keratinocyte growth factor analogue) was used as an adjuvant in the chemotherapy regimen to minimize the expected adverse effect of mucositis. The treating hematologists had reservations that palifermin may lead to the development of invasive squamous cell carcinomas (SCCs) within our patient’s DSAP plaques owing to its mode of action. Our patient noted marked and

Figure 1. Depicting extensive porokeratosis on the patient’s forearms.
sustained clinical improvement of his DSAP, likely owing to his chemotherapy for lymphoma and on follow-up had no clinical evidence of SCC twelve months post chemotherapy.

Case Synopsis
A 68-year old man with extensive DSAP was followed up over several years. His DSAP appeared prior to 30 years of age affecting all limbs and trunk. Diagnosis was made on clinical assessment by an experienced dermatologist with a positive family history of patient’s mother, maternal aunt, two of his siblings, and one of his two daughters also exhibiting identical DSAP lesions. He had no personal or family history of non-melanoma skin cancer or melanoma. Over time our patient’s DSAP dramatically worsened on both his forearms and lower legs intermingled with numerous hyperkeratotic actinic (solar) keratoses (Figures 1, 2). Marked facial papulopustular rosacea was noted with multiple actinic keratoses on his balding scalp. His actinic (solar) keratoses were treated with minimization of sun exposure and maximization of photo-protection, cryotherapy with liquid nitrogen, oral acitretin 10 mg daily, oral vitamin D 1000IU daily, and 15% salicylic acid in sorbolene cream to limbs daily after showering. His rosacea was treated with oral doxycycline 100 mg daily with topical metronidazole gel twice daily. The patient ceased acitretin treatment after approximately 12 months of treatment owing to adverse cutaneous side-effects while continuing with topical therapies. Hyperkeratotic actinic (solar) keratoses on his lower legs were treated with 20% salicylic acid in white soft paraffin under plastic wrap occlusion. Unfortunately the patient developed a primary CNS lymphoma six years after our initial review after noticing left sided visual disturbance. His diffuse B cell lymphoma was treated with intravenous methotrexate followed by oral busulfan. Palifermin (a novel recombinant human keratinocyte growth factor) was added to treatment with busulphan to limit mucositis, an undesirable but common side effect of our patient’s chemotherapy protocol [1]. A concern of the treating hematologists was that palifermin might lead to the development of invasive squamous cell carcinomas (SCCs) within our patient’s DSAP plaques given the increased risk conferred by DSAP [2]. During his chemotherapy and treatment with palifermin our patient noted marked clinical improvement of his DSAP, which we believe is secondary to the methotrexate and busulfan chemotherapy regimen. Follow-up of the patient for 12 months after chemotherapy has since shown a sustained near total clearance of his scaly plaques of DSAP and no SCCs have been detected (Figure 3).

Case Discussion
DSAP was first described by Chernosky in 1966 as an autosomal dominantly inherited cutaneous disorder, usually appearing between the 3rd and 4th decades [3]. The proposed pathogenesis of DSAP is a clonal proliferation of atypical keratinocytes that form a cornoid lamella after years of ultraviolet light

Figure 2. Depicting extensive porokeratosis on bilateral lower legs.

Figure 3. Clearance of disseminated superficial actinic porokeratosis twelve months following chemotherapy.
exposure. Ultraviolet light causes a mutation of DNA alongside a pre-existing copy of a mutated gene [4]. This is consistent with DSAP being observed more commonly in high sun-exposure countries such as Australia [3]. Classic DSAP presents as multiple annular, hyperkeratotic, pruritic, brown, flat papules and plaques measuring 2 to 10 mm in diameter in a photo-distribution pattern. The center of each flat papule or plaque is atrophic with a contrasting raised edge. The raised edge is consistent with the cornoid lamellae seen under histological examination. Classical DSAP spares the mucosal and palmar surfaces. Whereas DSAP is usually a benign disease the papules or plaques of DSAP have been reported to develop into squamous cell carcinomas (SCCs) or basal cell carcinomas (BCCs) [2]. Distribution is typically on extensor surfaces of legs, forearms, shoulders, and back with flares related to UV exposure [5]. Two case series of treatment of DSAP with topical diclofenac 3% gel twice daily showed varying results. The first study found positive results in seven of thirteen patients whereas the second study showed only mild improvement in two out of eight patients. Given the relative safety of non-steroidal inflammatory drugs the authors suggested a trial of topical diclofenac in patients with DSAP may be worthwhile as well as topical salicylic acid [4, 5]. Topical 5-Fluorouracil appears effective at aiding resolution of porokeratosis as described in multiple case reports as are topical and systemic retinoids. However, relapse on cessation has been reported along with exacerbation of porokeratoses during treatment [5]. Further topical treatments recommended include topical calcipotriol (a vitamin D analogue). Topical vitamin D induces keratinocyte differentiation. Another case series found a similar degree of benefit with daily topical calcipotriol combined with topical diclofenac for up to two months [6]. Photodynamic therapy (PDT) has also been to treat DSAP with variable results. One series of three patients showed little or no benefit whereas the second trial showed promising results in a single case [7]. Finally, two patients with DSAP treated with the Q switched ruby laser were reported. Both studies of treatment with the Q switched ruby laser reported remarkable results, which were replicated in one patient with CO₂ laser, two with erbium and neodymium YAG lasers, and two with fractional 1927-nm thulium fiber lasers [7]. However, caution must be used to generalize benefit owing to the limited series of patients, nature of multiple treatments required, and the significant cost of treatment with any laser therapy. Given the lack of randomized controlled trials and the lack of high quality evidence for the treatment of DSAP further research into treatment of this condition is warranted to provide better evidence-based management.

Two studies have detailed the use of palifermin to limit mucositis in patients undergoing treatment with chemotherapy. The first study conducted by Hille et al. explored the use of palifermin in head and neck cancer-related squamous cells concluded that there was no increased mitogenic activity from introducing recombinant keratinocyte growth factor (KGF) to human cells [8]. These results were replicated by Ning and colleagues in a separate study both in vivo and in vitro for head and neck squamous cell carcinoma [9]. Toriseva et al. performed extensive in vitro research detailing that recombinant KGF also appears to reduce gene expression of matrix metalloproteinase 13 (MMP-13), a gene associated with ability of tumor cells to undergo metastatic spread. MMP-13 is normally found to be expressed in higher amounts in SCC cells compared to normal epithelial cells. This observation led the authors to conclude that recombinant KGF could potentially suppress the malignant phenotype of SCC cells [10]. Disseminated superficial porokeratosis (DSP) has been observed to occur in a single patient with AIDS without significant actinic damage as well as a patient undergoing bone marrow transplantation with high dose radiation and chemotherapy induction [11, 12]. Our patient experienced clearing of his porokeratoses post chemotherapy and palifermin, leading the writers to suspect chemotherapy as the cause. To our knowledge, clearance of DSAP has not been previously reported with methotrexate or busulfan after extensive literature review. Case reports also exist for disseminated superficial porokeratosis occurring post cetorilizumab and methotrexate (not DSAP), [13]. The effect of methotrexate and busulfan is biologically plausible given the documented
efficacy of topical 5-fluorouracil and the likelihood that these aforementioned case patients may indeed have had DSP rather than DSAP owing to low actinic damage burden.

Conclusion
Although usually following a benign course, patients with DSAP can develop non-melanoma skin cancers (NMSC). We described a patient with longstanding hyperkeratotic DSAP of his forearms and lower legs who developed a primary CNS lymphoma treated with palifermin (a KGF analogue) as part of his chemotherapy to limit side-effects. He experienced marked clinical improvement of DSAP on his limbs during chemotherapy despite only mild improvement from previous topical therapies of salicylic acid. Follow-up after 12 months has shown a sustained clearance of his DSAP with no SCCs being detected. Literature investigating in-vivo and in-vitro supports safe use of palifermin in individuals at high risk of developing SCCs, and may even confer potential protection. Chemotherapy may disrupt clonal proliferation of atypical keratinocytes leading to clearance observed in this case. Further research into the interaction between KGF analogues and NMSC is warranted in addition to the interaction between chemotherapy and DSAP.

Abbreviations
Disseminated superficial actinic porokeratosis (DSAP); squamous cell carcinomas (SCCs); basal cell carcinomas (BCCs); keratinocyte growth factor (KGF); matrix metalloproteinase 13 (MMP-13); non-melanoma skin cancers (NMSC); central nervous system CNS.

References