Severe widespread actinic damage and squamous cell carcinoma: could hydrochlorothiazide be implicated? A report of two cases

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Introduction

Hydrochlorothiazide, a thiazide diuretic, is commonly prescribed for various indications including hypertension, cardiac failure and symptomatic oedema. There is emerging evidence (Shin et al, 2019) that this drug is associated with an increased risk of non-melanoma skin cancers, especially squamous cell carcinomas.

This article presents two cases of suspected hydrochlorothiazide-induced severe actinic damage and the subsequent development of squamous cell carcinoma.

Discussion

Hydrochlorothiazide is a thiazide diuretic used for various indications as it is inexpensive, effective and well tolerated. It can be used as monotherapy or in combination with other antihypertensives. In the UK, thiazide or thiazide-like diuretics are second line in the management of hypertension (Boffa et al, 2019).

Case report 1

A 90-year-old woman with Fitzpatrick skin type I and high natural sun exposure was diagnosed with hypertension in 1979. She was commenced on a combination of amiloride and hydrochlorothiazide at 5 mg and 50 mg respectively once daily. Her medical history included indolent chronic lymphocytic leukaemia diagnosed in 2003 and rectal tumour in 2015. She began to develop actinic damage initially in typical sun-exposed sites but this later became more widespread. In 2002, she developed squamous carcinoma in-situ and had subsequent Bowenoid lesions proving difficult to manage *(**Figures 1a–c**)*. Her first squamous cell carcinoma presented on her nose in 2011 and since then she has developed further lesions.

Conventional treatment with cytotoxic creams, photodynamic therapy and surgery has been of minimal benefit. At present, treatment is limited to managing only symptomatic or progressive lesions with surgical intervention.

Case report 2

A 59-year-old woman with Fitzpatrick skin type II is under the care of dermatology for widespread actinic damage *(**Figure 2**)*, initially thought to be secondary to chronic exposure to ultraviolet light. She was a regular sunbed user and enjoyed sunny holidays in her teenage years. When she developed her first non-melanoma skin cancer in her thirties this prompted further investigation. She was referred for phototesting which was negative. PTCH-1 gene and investigations for xeroderma pigmentosum and xeroderma pigmentosum-like variants were also negative. In 2014, she developed her first squamous cell carcinoma.

The patient has been on amiloride–hydrochlorothiazide combination therapy since the age of 26 years for fluid retention. Unfortunately, despite conventional treatment for her actinic damage and transplant-based oral chemoprophylaxis regimens (both acitretin and nicotinamide), she developed metastatic squamous cell carcinoma localised to her right axillary lymph nodes. There was no additional metastatic disease on staging computed tomography imaging. This area was subsequently treated surgically with node resection. She remains under close observation and skin surveillance.

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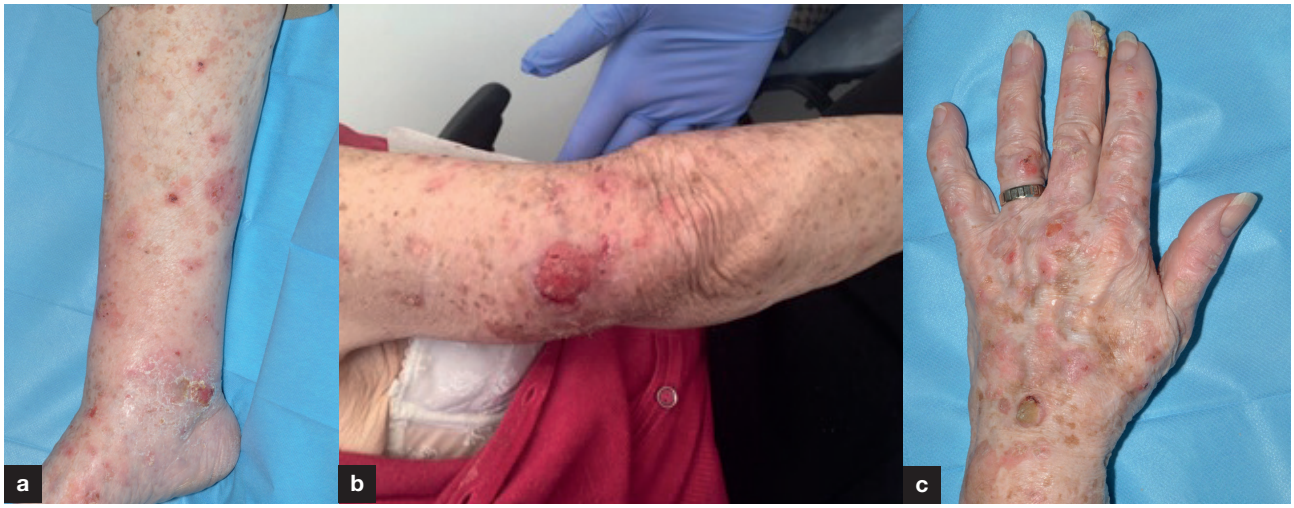

Figure 1. Widespread actinic damage on (a) lower and (b,c) upper limbs with (b) a biopsy-proven squamous cell carcinoma on the right elbow which was surgically excised.

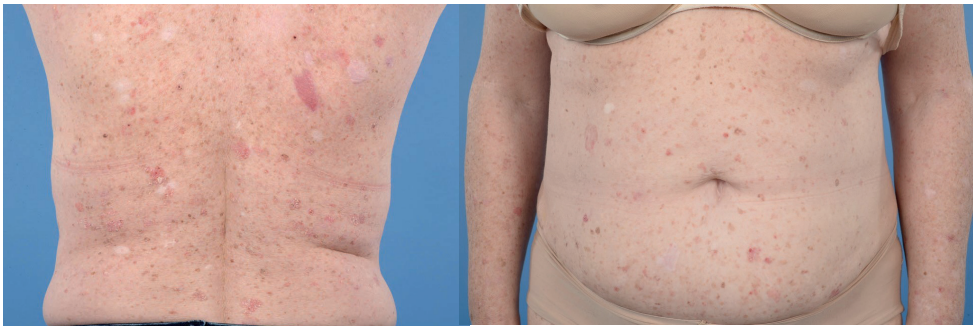

Figure 2. Severe actinic damage on anterior and posterior trunk with multiple Bowenoid lesions.

As a class effect, diuretics can be photosensitising agents. However, hydrochlorothiazide (sulphonamide-derived) in particular has been linked to the development of non-melanoma skin cancer (Jensen et al, 2008). It is now classed as a drug potentially carcinogenic to humans (Pedersen et al, 2018, 2019). Studies have suggested that it not only increases the risk of squamous cell carcinomas but also rare cutaneous malignancies such as Merkel cell carcinoma and malignant adnexal tumours (Pedersen et al, 2019). It has been suggested that the risk increases with higher cumulative doses and longer duration of use (Pedersen et al, 2018). More recently, the Medicines and Healthcare products Regulatory Agency in the UK has updated the drug safety profile of hydrochlorothiazide which echoes a similar message. They advise healthcare professionals to inform patients taking hydrochlorothiazide-containing products of this risk and the need for regular skin monitoring and sun protection, particularly in long-term use (DTB Team, 2019).

The exact mechanism of cutaneous carcinogenesis secondary to thiazides is not clearly understood. The theory is that the photosensitising trigger in combination with ultraviolet exposure enhances the risk of actinic damage which subsequently increases the risk of malignancy (Shin et al, 2019).

Both patients in this series were exposed to hydrochlorothiazide for a significant period of time. After extensive investigations for severe actinic damage and multiple non-melanoma skin cancers proved negative, the authors believe that hydrochlorothiazide had a significant role to play in the development of cutaneous malignancies. Clinicians should be aware of this potential adverse effect, and careful consideration should be given when prescribing this drug. An alternative antihypertensive agent should be considered in high-risk populations, ie patients who have a history of skin cancer. Patients who use this drug for a long period should be vigilant with skin monitoring and limit their exposure to ultraviolet light.

Learning points

- Hydrochlorothiazide has been linked to an increased risk of non-melanoma skin cancer.
- Hydrochlorothiazide is a widely used diuretic, so this is potentially an important public health concern.
- Healthcare professionals should educate patients who are taking this medication about the importance of regular skin checks and good sun protection measures.
- Use of alternative agents may be prudent in those with existing risk factors.

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References

Boffa RJ, Constanti M, Floyd CN, Wierzbicki AS; Guideline Committee. Hypertension in adults: summary of updated NICE guidance. BMJ. 2019 Oct 21;367:l5310. https://doi.org/10.1136/bmj.l5310

DTB Team. MHRA drug safety update: hydrochlorothiazide and non-melanoma skin cancer. Drug Ther Bull. 2019;57(5):70. https://doi.org/10.1136/dtb.2019.000023

Jensen AØ, Thomsen HF, Engebjerg MC et al. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. Br J Cancer. 2008;99(9):1522–1528. https://doi.org/10.1038/sj.bjc.6604686

Pedersen SA, Gaist D, Schmidt SA et al. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol. 2018;78(4):673–681. https://doi.org/10.1016/j.jaad.2017.11.042

Pedersen SA, Schmidt SA, Hölmich LR et al. Hydrochlorothiazide use and risk for Merkel cell carcinoma and malignant adnexal skin tumors: a nationwide case-control study. J Am Acad Dermatol. 2019;80(2):460–465. https://doi.org/10.1016/j.jaad.2018.06.014

Shin D, Lee ES, Kim J et al. Association between the use of thiazide diuretics and the risk of skin cancers: a meta-analysis of observational studies. J Clin Med Res. 2019;11(4):247–255. https://doi.org/10.14740%2Fjocmr3744