SKIN

BRIEF ARTICLE

Suspected Role of Long-term Anticonvulsant Use in the Development of Squamous Cell Carcinoma

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INTRODUCTION

Squamous cell carcinomas (SCC) are typically a tumor of advancing age (mean age at diagnosis: 70), with more than 80% of cases occurring among people aged 60 and older.[1] In addition, these cancers commonly appear on sun-exposed areas of the body such as face, ears, neck, non-hair bearing scalp, and dorsal aspect of extremities and hands.[2] Due to the rare presentation of SCC in a younger patient, secondary risk factors should be examined.

Many commonly used anticonvulsants, including lamotrigine and valproic acid, have known photosensitizing properties.[3] In susceptible patients, the long-term interaction between photosensitizing medications and UV radiation elevates risk of damage from the sun and has the potential to increase the likelihood of developing skin cancer over time.[4] There have been few studies that examine a possible association between anticonvulsants and various skin cancers, though the topic remains controversial and without consensus.

We report a 45-year-old woman who developed SCC on the scalp with a 10-year history of anticonvulsant use, including lamotrigine and valproic acid.

CASE REPORT

A 45-year-old woman, with past medical history of epilepsy and skin cancer presented with a 6-month history of non-healing skin lesion on the scalp **(Figure 1)**. She described the lesion as non-painful, but itchy, dry and flakey. Physical exam revealed an 8x15 mm pink, scaly plaque on left posterior scalp concerning for non-melanoma skin cancer. The lesion was sampled by shave biopsy and confirmed to be a well-differentiated squamous cell carcinoma via histological analysis **(Figure 2)**.

She had a history of actinic keratoses on the face and a biopsy-proven basal cell carcinoma on the shoulder all within the past 5 years, but no history of SCC prior to this and no first-degree relative history of skin cancer. She had no history of systemic immunosuppression and as part of her professional career had worked indoors for the past 5 years as a librarian. Her hobbies included recreational activities such as hiking, gardening and swimming, but she reported no other history of unusually intense sun exposure.

She had been taking Lamictal XR (lamotrigine) 200 mg/day for the past 10 years and Depakote (valproic acid) 600 mg/day for the past 6 years for seizure management, with no other medications.

For complete tumor extirpation, Mohs microscopic surgery was completed, demonstrating clear margins after one stage of surgery without complication. The patient was encouraged to discuss alternative pharmacological treatment options with the neurologist managing her epilepsy.

DISCUSSION

Squamous cell carcinomas occur less frequently than basal cell carcinomas, accounting for about 20% of skin cancers. The great majority of these cancers occur in elderly patients and on sun-exposed regions such as the face, lower legs, and forearms.[1] The aforementioned patient developed a squamous cell carcinoma of the scalp, an area well-covered with hair, at the age of 45. A large study examining patterns of 9,650 biopsied skin lesions found that only 6% of SCCs occurred in those under 50 years old and only 0.4% of SCCs found on women occurred on the scalp region.[2] Therefore, our patient represents an exceedingly rare presentation of SCC that may involve additional inciting risk factors.

In the above patient, we believe that long-term lamotrigine and valproic acid use may have contributed to the development of squamous cell carcinoma. Both lamotrigine and valproic acid are among the list of anticonvulsant medications classified as photosensitizing agents.[3,5] Valproic acid is often co-administered with lamotrigine for better management of epilepsy due to the synergistic effects. Additionally, when administered concurrently, valproic acid has been shown to increase steady state plasma concentrations of lamotrigine by more than 2-fold and increase the half-life of lamotrigine from 25 to 70 hours.[6,7] These increased lamotrigine levels and exposure could in turn increase the risk of photosensitivity reactions and additional sequelae, including skin cancers.

Photosensitizing drugs are exogenous chromophores that absorb photons of a specific wavelength, namely from sun exposure, leading to their activation. These photosensitive reactions can induce an inflammatory reaction (phototoxicity) or a T-cell medicated reaction (photoallergy).[4] Clinical manifestations of photosensitivity include pruritic eczematous lesions of photoallergy and/or “exaggerated sunburn”,

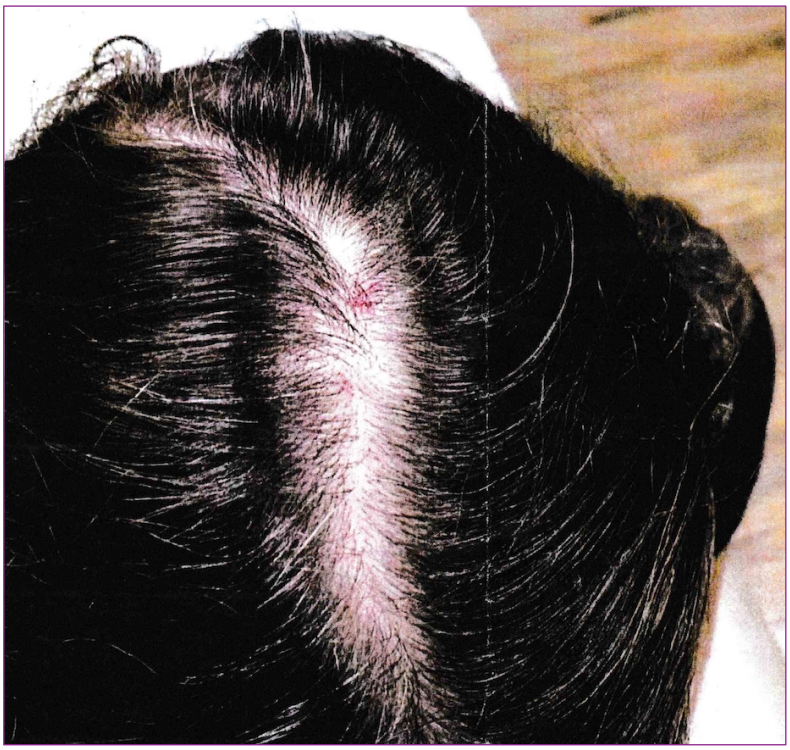

Figure 1. An 8x15 mm pink, scaly plaque on the left posterior scalp of a middle-aged woman.

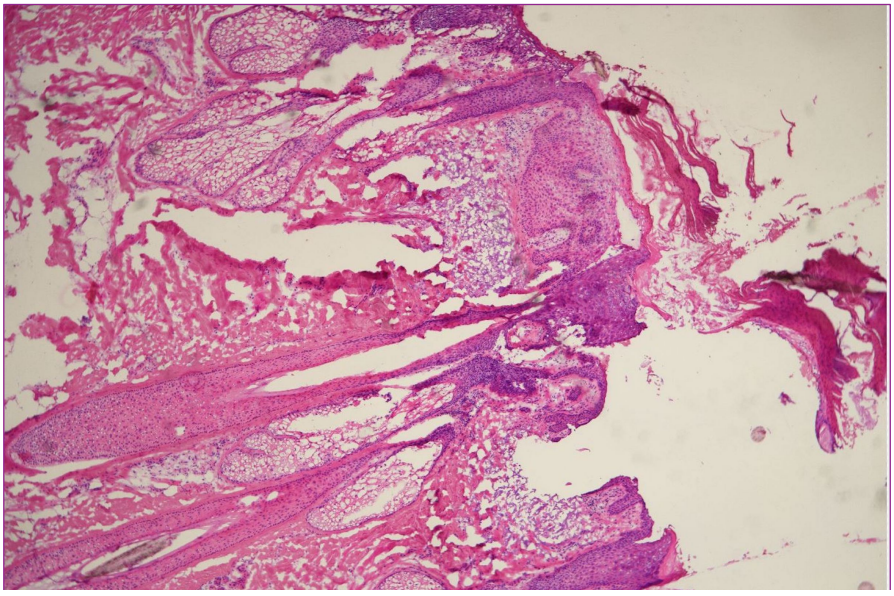

Figure 2. A shave biopsy submitted for H&E revealed a well-differentiated squamous cell carcinoma.

demonstrating phototoxicity.[4] The main environmental risk factor for skin cancer is UV radiation and since these drugs can increase the amount of UV absorption into the skin upon sun exposure (photosensitivity), it is plausible to implicate them in certain skin cancer etiologies.

There is good consensus that some other photosensitizing medications such as HCTZ are proven to increase risk of certain skin cancers due to their photosensitizing properties. Although this same consensus does not yet exist for the aforementioned anticonvulsants, there are a few studies that report an association between anticonvulsant use and skin cancer, but results are mixed. A recent large case-control study found that most antiepileptic drugs were not significantly associated with skin cancer. However, they found a significantly increased risk of SCC associated with the high use of lamotrigine (OR 1.57) and carbamazepine (OR 1.88), without any increased risk for BCC or melanoma.[8] Other studies, however, have shown significant associations between skin cancer and other individual anticonvulsants including valproic acid and carbamazepine, as well as anticonvulsants as a whole class.[9,10] Consequently, greater investigation within this area should be done.

Our patient is an important addition to the literature as an atypical case of SCC that could potentially be explained by lamotrigine and valproic acid use. Therefore, patients taking photosensitizing anticonvulsants like lamotrigine and/or valproic acid should consider discussing alternative medication options with their physician or be followed carefully for the development of skin cancer. Dermatologists should be aware of the association between these medications and photosensitivity with possible progression to non-melanoma skin cancer. Further, these patients should be counseled on proper sunscreen use, wearing a hat and protective clothing when outdoors in the sun and other UV protection methods.

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